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GASTRIC BIOPSY IN PEINICIOUS ANÆMIA.[1]

By R. K. DOIG[2] and I. J. WOOD,[2]

From the Clinical Researcl Unit of the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital.

WITH the development of a technique for blind gastric biopsy in the Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital, an unexpected result was the amount of information obtained in cases of pernicious anæmia and subacute combined degeneration of the cord. The part this technique can play in the early diagnosis of subacute combined degeneration of the cord has been discussed elsewhere (Doig *et alii*, 1950). It is the purpose of this paper to report the findings on gastric biopsy in patients with pernicious anæmia, particularly in relation to the effect of adequate liver therapy.

History of Gastric Biopsy.

The development of gastric biopsy began in New York with the observations of Einhorn in 1894. He saw fragments of gastric mucosa in the washings after gentle gastric lavage and examined them microscopically. In 1938 Hawksley, in London, independently observed similar fragments and made extensive histological studies (Hawksley, 1938; and Hawksley and Gooray, 1948). However, many of the fragments were necrotic and superficial, and little useful information was obtained. In 1906 Chevalier Jackson skilfully carried out gastroscopy with a rigid gastroscope and soon began to obtain biopsies from the mucosa of the body of the stomach using long biopsy forceps. In 1935 he reported that he had carried out hundreds of biopsies without a single complication (Jackson and Jackson, 1935). In 1946 Kenamore, Schiff and Womack described an operating gastroscope and obtained a limited number of biopsy fragments. Finally in 1948 Carmena d'Almeida, of Paris, and Benedict, of Boston, described more efficient gastroscopes fitted with biopsy forceps, which they claimed removed satisfactory fragments. It would appear that our flexible gastric biopsy tube is the first narrow-bore instrument to be described which can readily be passed with minimum discomfort and risk to the patient, and which gives a representative picture of the mucous membrane of the body of the stomach. It lacks, however, the advantage of siting the area from which the biopsy is being taken, although it is relatively easy to ensure that fragments are obtained from the body of the stomach. This has been confirmed in a few instances radiologically, in many instances by subsequent gastroscopy, and finally by the actual histological findings.

Instrument and Technique.

The flexible gastric biopsy tube used in the present investigation was designed in our unit and has been described in detail elsewhere (Wood *et alii*, 1949). Briefly, it consists of a length of Bowden wire covered by plastic tubing to render it airtight. Attached to the distal end of the tube is a small metal cylinder containing a cylindrical knife. This knife can be moved up and down past a lateral

[1] Read at a meeting of the Victorian Branch of the British Medical Association on April 5, 1950.

[2] Aided by a grant from the National Health and Medical Research Council.

hole by means of a long operating wire which protrudes from the upper end of the tube. The bottom end of the metal cylinder is sealed by a screw, which can readily be removed to inspect the cylindrical knife and obtain the biopsy fragment.[1]

Before the tube is passed the patient is prepared by anæsthetizing the throat with a cocaine spray and gargle, and emptying the stomach with a fine stomach tube. The resting juice is tested for free acid and its volume noted. The biopsy tube is then gently inserted into the stomach to about 50 centimetres. Negative pressure is exerted with a hand pump connected to the upper end of the tube, and this sucks a knuckle of gastric mucosa into the lateral hole. This is cut off by pulling up the cylindrical knife. The patient experiences no pain when the mucosa is cut. After withdrawal of the biopsy tube the fragment is obtained by removing the terminal screw and forcing out the cylindrical knife. The fragment, about one millimetre in diameter, is immediately placed in 10% formol saline solution and prepared for histological examination. Routinely the sections are stained by hæmatoxylin and eosin, by hæmatoxylin and mucicarmine, and by the special pepsin stain developed by Dr. R. Motteram, pathologist to our unit (Doig and Motteram, 1950).

With this technique 409 successful biopsies have been carried out on 345 patients in our unit. In the last 200 consecutive operations by one of us (R.K.D.), satisfactory specimens of gastric mucosa were obtained in 91% of cases.

With regard to complications, there was no evidence of perforation or established ulceration. Indeed, evidence is accumulating which leads us to believe that in both the cat (Gunter, 1950) and man, lesions in the gastric mucosa produced by this instrument are covered by epithelium in three or four days. The only complication was hæmorrhage, which produced obvious symptoms and signs in five cases out of 484 attempted biopsies. This occurred either as frank hæmatemesis or melæna. In no case did life appear to be threatened.

Gastric Mucosa in Pernicious Anæmia.

In 1870 Samuel Fenwick performed a post-mortem examination on a patient with "idiopathic anæmia" as described by Addison, and in the stomach found that "the whole of the glandular structure of the organ was in a state of atrophy". In his article he pointed out why he thought that post-mortem digestion had not affected his observations, and told how he demonstrated the loss of peptic activity. Magnus and Ungley (1938), Meulengracht (1939) and Cox (1943) confirmed the presence of atrophy in the body of the stomach in pernicious anæmia and also pointed out that the pyloric portion of the stomach was relatively normal. They have described in detail the histological features of the atrophic mucosa. Magnus and Ungley, and also Cox, realized that the characteristic of the mucosal change was an atrophy without evidence of old inflammation. Achlorhydria is now held to be an invariable accompaniment of pernicious anæmia (Wilkinson, 1949). We also believe that a diagnosis of subacute combined degeneration of the cord is untenable in the absence of achlorhydria.

By means of gastric biopsy we have been able to study the mucosa in 33 cases of pernicious anæmia during life. We have used the term gastric atrophy to describe the typical appearance of the mucosa. We have found that the distinction between gastric atrophy and chronic atrophic gastritis can be drawn in the vast majority of cases.

In pernicious anæmia, and also in subacute combined degeneration of the cord, the mucosa was usually thinner than normal, even to being less than half the average depth. There was almost complete atrophy of the gastric glands (of the body), so that in but very few cases were there any pepsinogen granules in the pepsinogen-stained section. The surface epithelium usually showed intestinal metaplasia with numerous goblet cells, and when some residual gastric epithelium was present it was of tall columnar type, with the same uniform appearance as in normal mucosa (Doig and Motteram, 1950). There was some cellular infiltration of the *lamina propria*, chiefly with lymphocytes, but either was it dense, nor were there polymorphonuclear leucocytes. These features are illustrated in Figures II, IV, V and VI.

By contrast, in chronic atrophic gastritis (Doig, 1949) the mucosa showed more variable reduction in depth, and it was common to find residual clumps of chief and parietal cells. Intestinal metaplasia was not frequent, and the surface epithelium was usually irregular in height and staining qualities. The cellular infiltration in chronic atrophic gastritis was dense, and lymphocytes, plasma cells, polymorphonuclear cells and macrophages could always be found.

The following patient had the typical findings in biopsy material.

CASE I.—Mr. H.M., aged forty years, was referred for gastric biopsy because of dyspepsia for two years. During that time the result of barium meal examination had been normal twice and he had achlorhydria with gruel. Over twelve months of observation he had numerous attacks of upper abdominal discomfort and bloating, with flatulence. These attacks lasted a week. There was increased discomfort with eating. He had histamine-fast achlorhydria and on gastric biopsy atrophic gastritis (see Figure II).

The preliminary emptying of the stomach also provided another difference between the two conditions. In gastric atrophy, the average fasting content removed was five millilitres, and in atrophic gastritis it was ten millilitres. With normal mucosa, including duodenal ulcers, the fasting content averaged 34 millilitres. Gastric atrophy was always accompanied by histamine-fast achlorhydria, atrophic gastritis almost always so. Another cause of persisting histamine-fast achlorhydria was superficial gastritis. The essential feature in this condition was that the main inflammatory changes were in the superficial portion of the mucosa, and little or no loss of gastric glands had occurred. Clinically and histologically it was a forerunner of atrophic gastritis.

Of the histological features in the gastric atrophy of pernicious anæmia, perhaps the most striking was the intestinal metaplasia (Magnus, 1937), although it is important to remember that it is not completely diagnostic of pernicious anæmia. Not only did the intestinal epithelium show numerous goblet cells, but the arrangement often suggested intestinal crypts. A typical striated border was present, and the change from gastric to intestinal epithelium was quite abrupt.

Some years ago it was suggested that an absence of argentaffin or Kulschitzky cells was a feature of pernicious anæmia (Jacobson, 1939). We have had no difficulty in demonstrating them in cases of pernicious anæmia with metaplasia. This confirmed the opinion of Magnus (1937, 1940). Recently the link of these cells with the mechanism of the development of the anæmia has been broken by the demonstration that these granules are not related to the pterins as is folic acid (Gomori, 1948). Lastly, Paneth cells, which are a characteristic of intestinal epithelium, could be demonstrated in the areas of intestinal metaplasia when stained with phosphotungstic acid and hæmatoxylin.

This differentiation between gastric atrophy and chronic atrophic gastritis was based on a study of all the biopsy specimens from cases of pernicious anæmia and subacute combined degeneration of the cord which we have obtained. In pernicious anæmia these biopsies have been carried out either before giving liver or only a few days after (17 cases), three to six months after the institution of treatment (five cases, four of which were for the second time), or after a varying number of years (15 cases), ranging from one year to twenty-five years and averaging five years. In the latter two groups we have seen nothing to suggest that there has been any regeneration whatsoever of the chief or parietal cells.

The following cases illustrate this constancy of histological appearance.

[1] The flexible gastric biopsy tube is being manufactured by Felton, Grimwade and Duerdins Proprietary, Limited, 21 Alfred Place, Melbourne.

Case II.—Mr. A.M., aged forty-five years, six months after a typical attack of infectious hepatitis reported to his doctor with weakness and loss of energy. He was referred to the Clinical Research Unit as a possible sufferer from chronic hepatitis. Apart from some pallor, he had mild atrophy of the tongue. The results of liver function tests and liver biopsy were normal. A routine blood film showed macrocytosis. There was histamine-fast achlorhydria and the blood and bone-marrow findings were typical. The disease was of moderate severity, the hæmoglobin value being 7·5 grammes *per centum*. Gastric biopsy showed atrophic mucosa (see Figure III). After six months' treatment with a complete clinical and hæmatological remission, the picture was unchanged (see Figure IV). In both sections the mucosa was thin, and there was complete atrophy of the gastric glands, with intestinal metaplasia and minimal cellular infiltration.

Case III.—Mr. G.N., now aged sixty-one years, was admitted to the Royal Melbourne Hospital in 1936, under the care of Dr. Hume Turnbull, with typical pernicious anæmia. He was the first patient at the hospital to have intramuscular injections of liver extract. Since then he has been adequately treated with liver extract ("Campolon" and "Anahæmin"). Gastric biopsy in 1949 showed the typical atrophic mucosa (see Figure V).

Case IV.—Mr. C.M., aged sixty-three years, in 1924 complained of weakness and anæmia for one year. He was treated irregularly with raw liver and desiccated hog's stomach up to 1936. He was then started on injectable liver extracts. Since 1936 he has been adequately treated and his hæmoglobin level well maintained. Gastric biopsy showed the same picture of atrophy (see Figure VI).

Thus we see that treatment for a shorter or longer time had no effect on the histological appearance of the mucosa in this group of 33 patients. In saying this we are completely at variance with some gastroscopists, who have reported a return of the normal appearance in a considerable percentage of cases (Hardt *et alii*, 1948; Schindler and Serby, 1939).

This finding of gastric atrophy on biopsy in pernicious anæmia and subacute combined degeneration of the cord is of the greatest value from the diagnostic point of view. The most important aspect of the diagnosis of anæmia is the accurate assessment of changes in the blood and bone marrow. Unfortunately, patients may be referred to hospital after treatment of anæmia with liver extract, based on inadequate examination of the blood. The certain diagnosis of pernicious anæmia then becomes difficult or impossible, apart from withholding treatment and waiting for definite changes to reappear. This is a risky procedure, for subacute combined degeneration of the cord may develop in the interim. Gastric biopsy provides a characteristic finding in the disease which is unaltered by treatment. In cord degeneration this problem can be almost completely met by consideration of the history and findings on examination of the nervous system.

Of 46 patients with pernicious anæmia or cord degeneration, in only three was the biopsy fragment not completely typical. In one of these the diagnosis of combined degeneration of the cord was by no means conclusive. In the other two there was some degree of polymorphonuclear infiltration. On the other hand, two patients showed gastric atrophy without either disease. One was a young man with achlorhydria to histamine but no other signs (Doig *et alii*, 1950). The other was a man aged sixty-five years with a long history of indigestion. He had some tingling in the feet, but only minimal objective signs as yet.

Summary.

1. By means of gastric biopsy we have separated three types of diffuse change in the gastric mucosa—superficial gastritis, atrophic gastritis and gastric atrophy.

2. Superficial gastritis and atrophic gastritis represent early and late stages of the one inflammatory process and are frequently associated with flatulent dyspepsia and achlorhydria.

3. Gastric atrophy can usually be separated from chronic atrophic gastritis by the relative absence of inflammatory changes, the more complete nature of the atrophy and the greater incidence of intestinal metaplasia of the epithelium.

4. Gastric atrophy is almost invariably accompanied by pernicious anæmia or subacute combined degeneration of the cord, and these diseases are rarely present in its absence.

5. Gastric atrophy is unaffected by adequate treatment with liver extract.

6. Gastric biopsy could be helpful in the diagnosis of pernicious anæmia when liver therapy has been given without an adequate hæmatological examination.

Acknowledgements.

We are indebted to Dr. R. Motteram, pathologist to the Clinical Research Unit, for his help in the morbid histology. Our thanks are also due to other members of the unit and to the honorary medical staff of the Royal Melbourne Hospital, in particular Dr. John Bolton. The photomicrographs were prepared by Mr. H. Matthaei, of the University of Melbourne.

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Legends to Illustrations.[1]

FIGURE I.—*Normal gastric mucosa.* The chief or pepsinogen-secreting cells stain black, since the granules take up the dye specifically. The parietal cells are situated mostly in the intermediate zone of the section. The epithelium of the surface and gastric pits is tall and regular. There is very little cellular infiltration in the *lamina propria*. (Pepsinogen stain × 125.)

FIGURE II.—*Case I. Mr. H.M., aged forty years.* Atrophic gastritis. There is a great reduction in the chief and parietal cells of the gastric glands. The surface epithelium is irregular, with some vacuoles containing polymorphonuclear cells. The pits have extended downwards irregularly. There is an increase in cellular infiltration with all types of cells. (Pepsinogen stain × 125.)

FIGURE III.—*Case II. Mr. A.M., aged forty-five years.* Gastric atrophy of pernicious anæmia prior to treatment. There is complete disappearance of gastric glands and reduction in depth. Almost all the surface epithelium is intestinal in character with striated border and numerous goblet cells. The *lamina propria* shows an increase in cellular infiltration, but no polymorphonuclear cells are present. (Hæmatoxylin and eosin stain × 125.)

FIGURE IV.—*Case II. Mr. A.M., aged forty-five years.* Gastric atrophy of pernicious anæmia after treatment with liver for six months. There is no change in the histological appearance. The abrupt change from gastric to intestinal epithelium is seen in the top centre. (Hæmatoxylin and eosin stain × 125.)

FIGURE V.—*Case III. Mr. G.N., aged sixty-one years.* Gastric atrophy of pernicious anæmia after adequate treatment for thirteen years. There is no change in the histological appearance. This section has been stained to show an absence of any pepsinogen granules in the atrophic mucosa. (Pepsinogen stain × 125.)

FIGURE VI.—*Case IV. Mr. C.M., aged sixty-three years.* Gastric atrophy of pernicious anæmia; first diagnosed twenty-six years ago; adequate treatment for fourteen years. The histological appearance is similar. However, most of the epithelium is gastric in type, with an islet of intestinal change in the centre of the field. (Hæmatoxylin and mucicarmine stain × 125.)

SARCOIDOSIS: A SURVEY, WITH REPORT OF THIRTY CASES.

By BRUCE ROBINSON and ALLAN W. POUND,
From the Pathology Department, The University of Melbourne.

Introduction.

THE Conference on Sarcoid of the National Research Council, Washington, on February 11, 1948, gave the following definition of sarcoidosis:

> Sarcoidosis is a disease of unknown ætiology. Pathologically it is characterized by the presence in any organ or tissue of epithelioid cell tubercles with inconspicuous or no necrosis and by the frequent presence of refractile or apparently calcified bodies in the giant cells of the tubercles. The characteristic lesions may be replaced by fibrosis, hyalinization or both.
>
> Clinically, the lesions may be widely disseminated. The tissues most frequently involved are the lymph nodes, lungs, skin, eyes and bones, particularly of the extremities.
>
> The clinical course usually is chronic, with minimal or no constitutional symptoms; however, there may be acute phases characterized by a general reaction with malaise and fever. There may be signs and symptoms referable to the tissues and organs involved.
>
> The intracutaneous tuberculin test is frequently negative; the plasma globulins are often increased.
>
> The outcome may be clinical recovery with radiographic evidence of residue, or impairment of function of organs involved, or a continued chronic course of the disease.

Although local manifestations of this disease had been described, it was not until the publication of the definitive article of Jörgen Schaumann, "*Sur le lupus pernio*" (1914), that the condition was fully recognized to be a generalized disease affecting internal organs as well as the skin.

Prior to this, Cæsar Boeck (1899), a dermatologist of Christiania, had described a patient, a policeman, aged thirty-six years, in good health, with peculiar skin lesions on the scalp, face, trunk and extremities. These cutaneous nodules were of three varieties. Some were slightly elevated, firm, "yellowish-brown" spots varying in size from that of a pea to that of a small bean, slightly scaling and penetrating deeply into the substance of the skin. Others were large nodules tinted bluish-red in the centre. There were also large, deeply infiltrated, bluish-red patches of irregular contour with prominent vessels running over their surface. Boeck thought these lesions to be "of very characteristic appearance", and observed that they retrogressed in one place, leaving thin atrophic scars, to appear in another. He noted that the patient had enlarged lymph nodes, but was never able to palpate his spleen. His was the first description of the histology of the lesions, which he described as "sharply defined foci of a newgrowth disseminated through the dermis". The cells were "of epithelioid type" with large vesicular nuclei, sometimes multiple, but with no mitoses. He noticed a few giant cells and observed that in some lesions collagen was being laid down. He could find no organisms in the sections and suggested that cultures should be made. He thought the appearance resembled sarcoma and therefore named the condition multiple benign sarcoid of the skin.

Boeck followed this case for at least five years, during which time the patient remained well but still retained his lesions. This man was seen and described many years later by Danbolt (1947) at the time of his final illness. He died at the age of eighty years in the Hospital of the Oslo University, as the result of a carcinoma of the left kidney. No demonstrable signs of sarcoidosis were found at that time in life or at autopsy.

Boeck (1905, 1916) retained his interest in this condition and observed over twenty cases. By this time he was convinced that it was a generalized disease—a concept that he had already hinted at in his first article and had elaborated further in later ones. He described lesions in the skin, lymph nodes, mucous membranes and other organs, and made further descriptions of the histology. As a result of this he revised his conception of the nature of the condition to regard it as related to, if not identical with, tuberculosis and renamed it benign miliary lupoid (1916).

Some years prior to Boeck's first article, E. Besnier (1889), a French physician, had described a patient with large, symmetrical, non-ulcerating, violaceous swellings of the nose, ears and fingers, striation of the nails and enlargement of the lymph nodes. He called the condition *lupus pernio*—the chilblain lupus.

Even earlier, Jonathan Hutchinson (1877) had described a man whom he had seen in 1869 with peculiar dark purple skin lesions, both diffuse and nodular. In retrospect this appears to be the first case of cutaneous sarcoidosis to have been recorded in the literature. In 1898 he described "Cases of Mortimer's Malady", which also appear to be the same disease. Referring to one of these, Boeck (1899) said: "I dare not say that his and my case are identical, as there are no histological studies by Hutchinson, but nevertheless I am inclined to believe that they are variants of the same group of diseases." A comment of Hutchinson (1898) is of interest in this respect. The patient, Mrs. Mortimer, "was presented at one of the meetings of the Dermatological Society of London. The general opinion was, I believe, that the disease was sarcoma, and it was strongly urged that portions should be removed for microscopic examination. This I subsequently suggested to my patient, and with the result that I did not see her again for two years"; an experience with which we are not unfamiliar in some of our own cases.

Independently of the above workers, Robert Kienböck (1902), an Austrian radiologist, described curious cyst-like lesions in the phalanges, although he was ignorant of their significance. Kreibich (1904) and Rieder (1910), in articles on *lupus pernio*, described similar bone changes and noted their relation to that disease, and Darier and Roussy (1906) described nodular subcutaneous lesions with the histological appearance described by Boeck.

In Schaumann's thesis "*Sur le lupus pernio*" (1914) these localized manifestations were demonstrated to be parts of a widespread systemic disease. He showed that the lymph

[1] In Case I (control) the result of the test meal was normal. In Cases II, III and IV achlorhydria was present.

ILLUSTRATIONS TO THE ARTICLE BY DR. R. K. DOIG AND DR. I. J. WOOD.

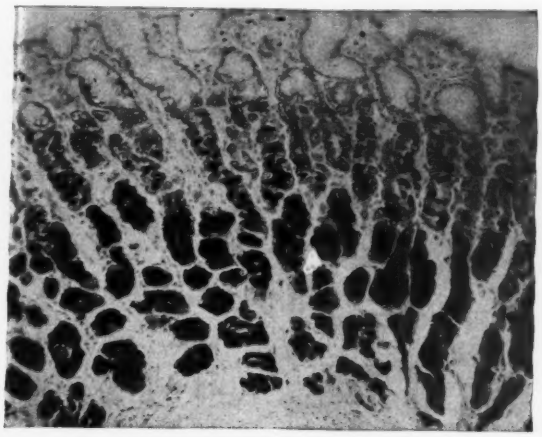

FIGURE I.

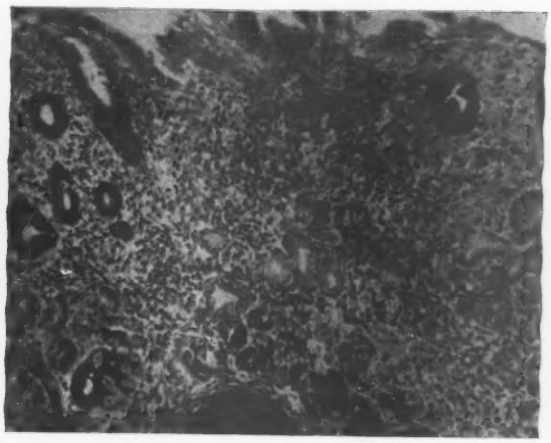

FIGURE II.

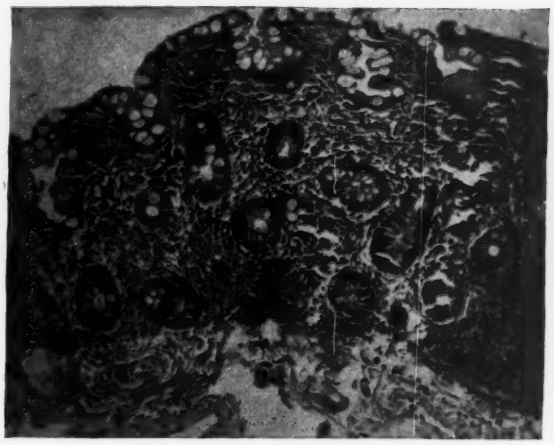

FIGURE III.

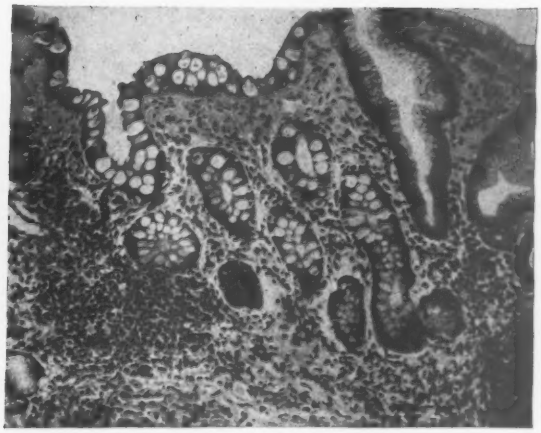

FIGURE IV.

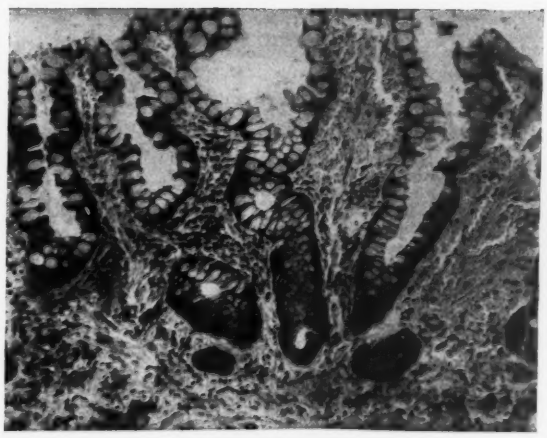

FIGURE V.

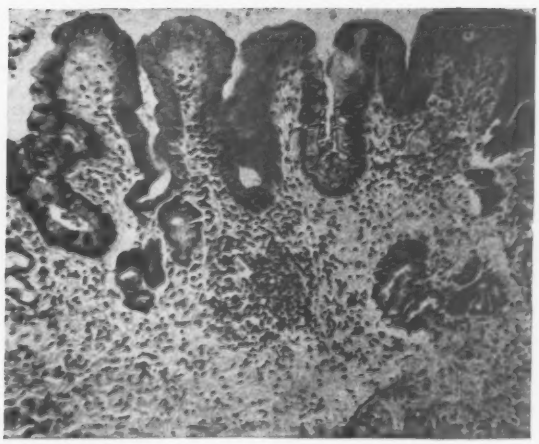

FIGURE VI.

ILLUSTRATIONS TO THE ARTICLE BY DR. BRUCE ROBINSON AND DR. ALLAN W. POUND.

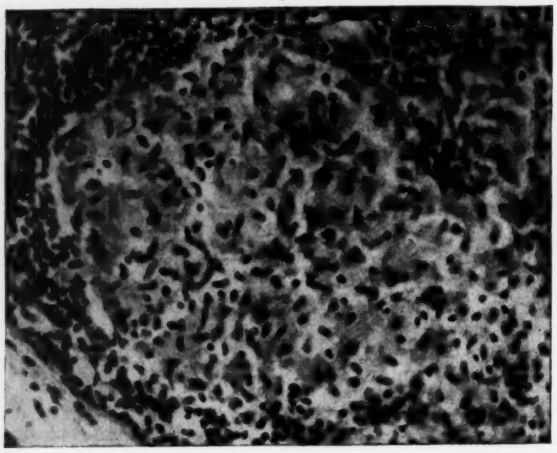

FIGURE I.

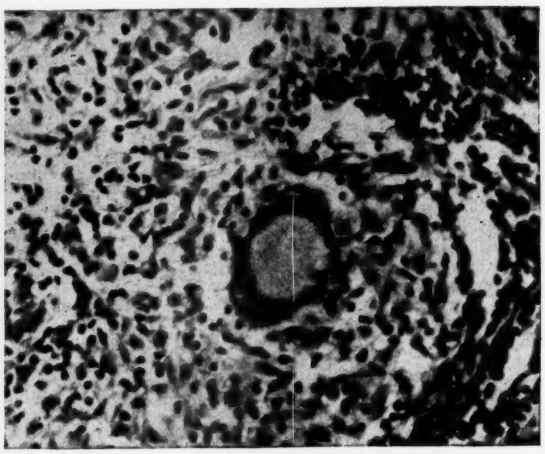

FIGURE II.

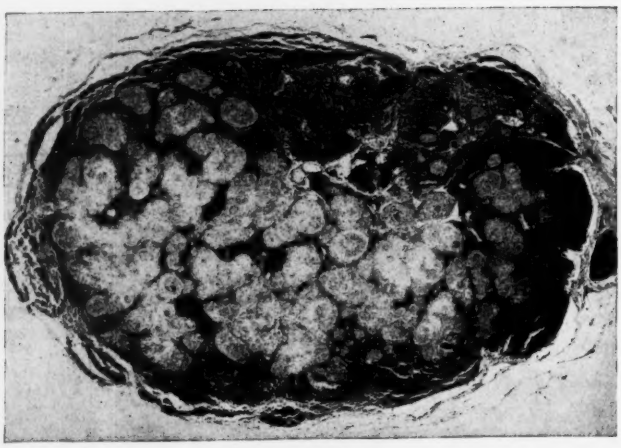

FIGURE III.

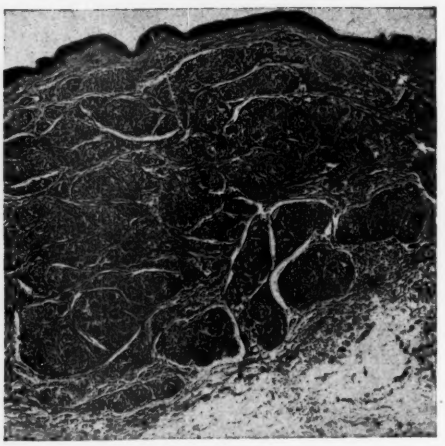

FIGURE IV.

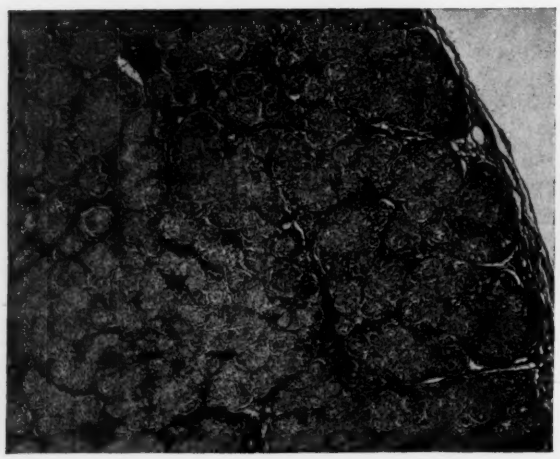

FIGURE V.

FIGURE XIV.

ILLUSTRATIONS TO THE ARTICLE BY Dr. BRUCE ROBINSON AND Dr. ALLAN W. POUND.

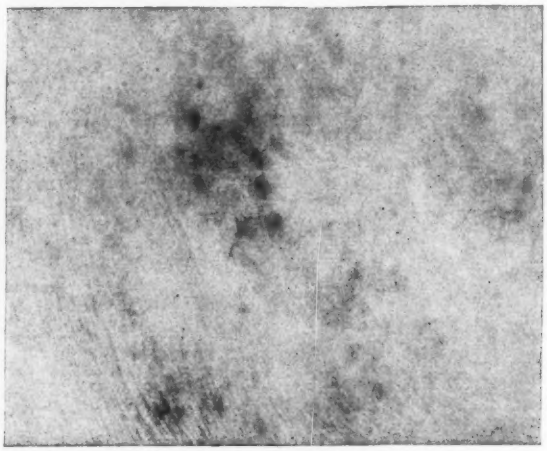

Figure XVI.

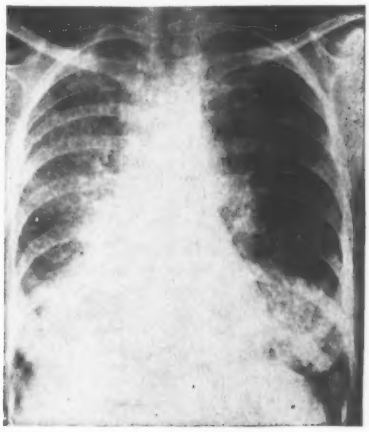

Figure XVII.

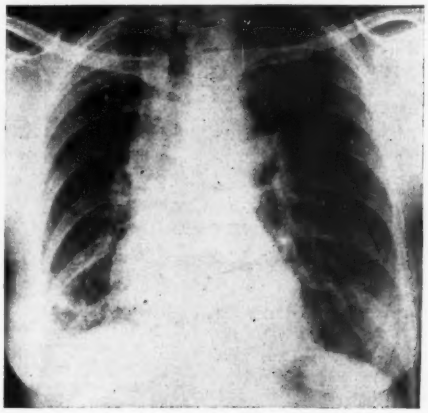

Figure XVIII.

Figure XX.

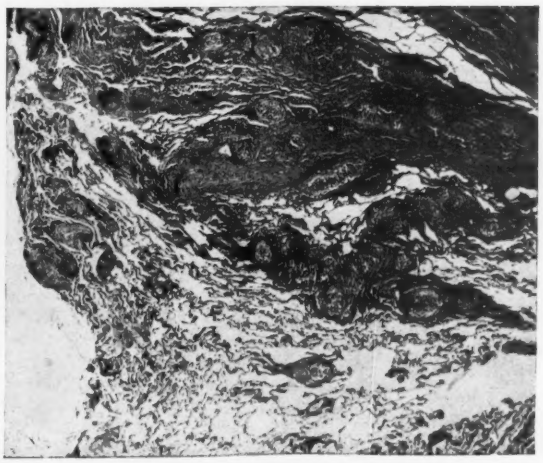

Figure XIX.

ILLUSTRATIONS TO THE ARTICLE BY DR. WARREN SMITH.

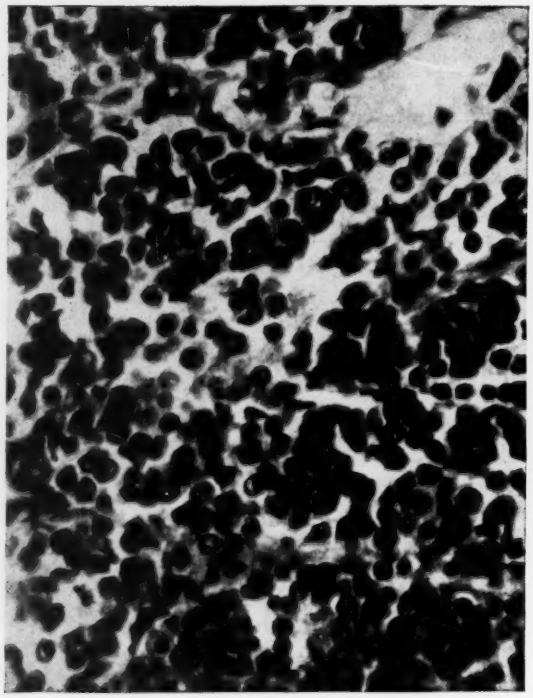

FIGURE III.
Autopsy specimen, sternal marrow.

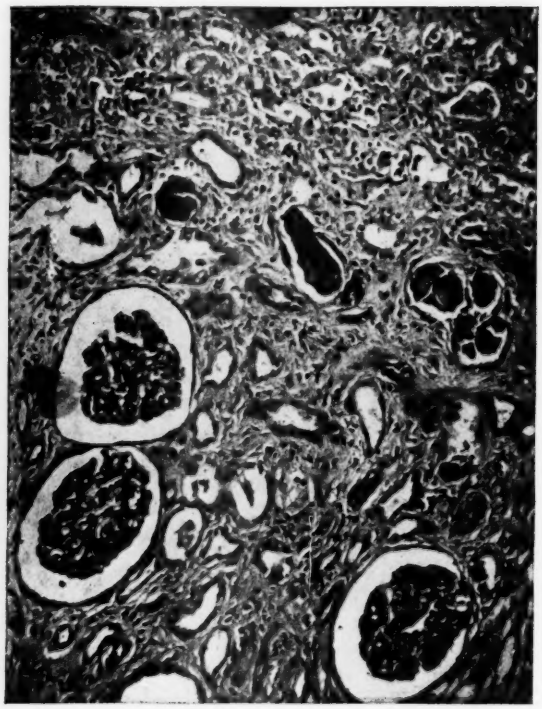

FIGURE IV.
Kidney.

ILLUSTRATIONS TO THE ARTICLE BY DR. GORDON KERRIDGE.

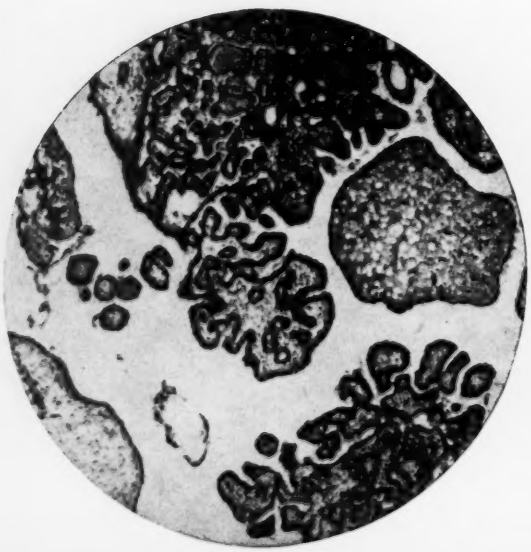

FIGURE I.
Photomicrograph (× 85) showing section from tumour of neck.

FIGURE II.
Photomicrograph (× 85) showing section from nodule in left lobe of thyreoid.

nodes, skin, lung, liver, spleen and bone might all be involved in association or independently. He described the X-ray appearance of "an abundant spotted infiltration of the lungs" with enlarged mediastinal lymph nodes, occurring in a symptomless patient who had no abnormal pulmonary signs. He showed that the histological picture described by Boeck in the skin was also to be found in the lymph nodes, lung and bone, and thus demonstrated the generalized nature of the disease, which he believed to be one of "lymphadenitic" nature. He continued this work for many years, and it is largely due to the reiteration of his views that the concept of the generalized nature of sarcoidosis has been accepted. He made many cultural and immunological studies, and believed that the disease was a peculiar form of tuberculosis, although he was rarely able to demonstrate the tubercle bacillus and believed that the absence of tuberculin sensitivity was an essential part of the syndrome (1924, 1936).

The radiological appearances in the chest were elaborated by Kuznitzski and Bittorf (1915), while Otto Jüngling (1920, 1928), a German surgeon, gave classical descriptions of the phalangeal lesions, observing the sparing of the joints and periosteum. From histological studies Jüngling concluded that the process was a peculiar form of tuberculosis and so named it *ostitis tuberculosa multiplex cystoides*.

A Danish ophthalmologist, C. F. Heerfordt (1909), had described a febrile disturbance associated with uveitis, cranial nerve palsies, salivary gland enlargement and a pleocytosis of the cerebro-spinal fluid, and it is now realized that some cases of this syndrome, in whole or in part, are due to sarcoidosis.

Since Schaumann's original article a voluminous literature has grown up, and lesions in nearly every tissue and organ have been described. It is not proposed to enumerate these or to discuss them further, except to draw attention to the reviews in English of Pinner (1938), Longcope (1941), Freiman (1948), Reisner (1944) and Harrell (1940); Hunter's review (1936) of the early history is of interest. In the Australian literature cases have been described by Lambie (1940), Frank (1942), Hurley and Hughes (1942), Counsell and Hamilton (1945), Ryan and Counsell (1945) and Isbister (1945).

In this historical review the important syndromes have been mentioned and attention has been drawn to the general nature of the disease. The duration is variable, and while signs may be notable and conspicuous, symptoms are few or absent. Unless an organ is of small compass, such as the eye, the pituitary gland or the bundle of His, it may be extensively involved with little functional or symptomatic disturbance. The sexes are equally affected. The disease may occur at any age, although it is most common in the middle years of adult life.

No cause for sarcoidosis has been established, but the theories regarding its nature fall into three main groups. The first is that it is a form of tuberculosis, and the second that it is a disease *sui generis* and is possibly due to a virus. The third or eclectic view is that this disease is a non-specific response which may be engendered by a variety of stimuli. No useful purpose is to be served by entering into any polemical discussion of these at this point—they are discussed by Pinner (1946), Pautrier (1948) and Freudenthal (1948).

It is apparent from the manner in which our knowledge of this condition has grown up that a huge nomenclature may have accumulated. The more commonly used names for the condition have already been indicated. The terms sarcoidosis, sarcoid, benign lymphogranulomatosis, non-caseating tuberculosis, *lupus pernio*, and uveo-parotid fever are also used, and are either descriptive or based on some unproven ætiological concept.

In this article the term sarcoidosis will be used, being convenient, non-committal and well-recognized.

The Histology of Sarcoidosis.

The characteristic histological lesion throughout the tissues involved in this condition is a follicle composed of large, pale, endothelioid cells, without central necrosis and with little surrounding lymphocytic accumulation (Figure I).

Contained in this follicle there are often multinucleated giant cells of foreign body (Langhans) type, with pale-staining cytoplasm similar to that of the endothelioid cells (Figure II). In some cases these giant cells are numerous, but in others they may be absent, their presence not being essential to the diagnosis. "Inclusion bodies" of various types have been described in or associated with these giant cells, but they are not invariably present and therefore cannot be a specific feature of the condition.

Between the endothelioid cells of the follicles there is a fine network of reticulin fibrils demonstrable by appropriate staining methods, such as silver impregnation. This is invariably present in this condition. However, it does not form a diagnostic criterion in differentiating the condition from the chronic lesions seen in other tuberculoid granulomata. The above follicular arrangement of endothelioid cells is the usual appearance. A variation sometimes occurs where sheets of endothelioid cells are seen in the absence of the predominant follicular arrangement.

The manner of development of the follicles is not known with certainty, but initially there appears to be an accumulation of mononuclear cells of histiocytic type with a few lymphocytes; the character of this cell accumulation changes with transformation of the histiocytic cells into endothelioid cells and formation of the classical follicular structures. Nor is their subsequent course known with any degree of prognostic reliability. The lesions apparently may persist *in statu quo* for long periods of years or may resolve, leaving little histological residue, in a period of months. On the other hand, with progress of time, collagen may be laid down between the endothelioid cells, with the result that the follicles become transformed into masses of relatively acellular fibrous tissue.

From what is known of the behaviour of these lesions, it is clear that in their development, structure and course they conform to the general pattern of tissue changes of known ætiology that result in the production of the endothelioid tuberculoid granulomata. However, although the granulomatous nature of these lesions is clearly evident, stains, cultures and animal inoculations usually fail to reveal any possible ætiological agent.

The tuberculoid granuloma described above is found in any tissue affected with the disease, irrespective of variation of clinical manifestation. The follicles may occur as isolated lesions scattered in a tissue (Figures III and XIX), as conglomerate masses (Figure IV), or in such numbers as to replace completely the normal structure of the part by a mass of closely packed tubercles (Figure V). In the tissues they are frequently scattered in relation to lymphatic or perivascular spaces, or around differentiated structures, such as hair follicles and sweat glands in skin. Individual follicles vary little in size, although cellular lesions may be found alongside lesions undergoing fibrosis (Figure XIX). Fibrosis in an extensively involved tissue, such as lung, uveal tract, nasal mucosa or skin, may lead to diffuse scarring.

This histological picture occurs with great regularity throughout the biopsy material obtained from the patients in the cases here reported. It clearly differentiates the disease from other conditions that may also result in a somewhat analogous group of clinico-pathological syndromes, such as Hodgkin's disease, lymphosarcoma, the leuchæmias and the other less well-defined "reticulo-endotheliosses". We have found that where any doubt has been raised in our minds as to the histological diagnosis of this "sarcoid reaction" the ultimate diagnosis has proved to be that of some other condition.

It is essential to point out that this picture, although typical, is not specific to this peculiar disease. We have seen such non-caseating tubercles in material from patients with leprosy, lipoid pneumonia, foreign body granulomata and brucellosis; they are described as occurring commonly in cases of beryllium poisoning and some fungous infections, occasionally in the lesions of *lymphogranuloma inguinale* and typhoid fever, and rarely in syphilis, Leishmaniasis and other chronic infections. However,

these conditions differ in their natural history, and the diagnosis is usually made by other means.

Differentiation from the usual histological reaction in tuberculosis with caseous necrosis and demonstrable bacilli does not constitute any diagnostic difficulty. However, the histological lesion of tuberculosis may not show any necrosis, and bacilli may not be demonstrable, even on culture and guinea-pig inoculation. Moreover, some cases of sarcoidosis typical in every other respect do show evidence of breakdown in the centre of the endothelioid cell follicles. Indeed it is clear that there is no sharp dividing line between the granuloma of tuberculosis and that of sarcoidosis, but that, if sought, a series of cases will be found showing in the structure of the lesions all gradations between those typically shown in the two conditions.

We are of the opinion that there is no histological means of distinguishing the condition of sarcoidosis from such non-caseating granulomata of tuberculosis apart from the demonstration of the tubercle bacillus.

Speaking from the histological viewpoint alone, it is only possible to state that a particular lesion shows a "sarcoid structure". The diagnosis of sarcoidosis is to be made only by taking into account the biological behaviour of the condition.

The Nature and Scope of this Investigation.

Three years ago an investigation was commenced at the pathology department of the University of Melbourne into the natural history of sarcoidosis. Particular attention has been paid to clinical and pathological aspects. In a chronic disease of this character, prolonged observation is necessary, and it is proposed that this investigation will be an extended one.

The cases have been gathered from a variety of sources, the patients representing a wide range of social and occupational groups. When the investigation was begun, the records of the public hospitals and of the Repatriation Department were examined and cases collected from them. Later on, patients with known and suspected sarcoidosis were referred by practitioners in town and country. Help has also been given by the directors of the Victorian Tuberculosis Bureau and their Mass X-Ray Survey Division. In four cases previously described by Frank (1942) the patients were traced and reexamined. They are Cases 13, 18, 20 and 32.

In all, 75 patients were examined. Of these, 30 have been proved to have sarcoidosis, and their histories will be found summarized in Table I. Seven other cases that present features for discussion are mentioned in the body of the article. These and the remaining cases have been used as a basis for the discussion of the differential diagnosis of the condition.

In this survey of the 30 confirmed cases an attempt is being made not to review all aspects of the disease, but rather to describe those features that were observed in our patients.

Diagnostic Criteria.

As the ætiology of sarcoidosis is unknown, criteria of diagnosis are necessary. Those used were as follows: (i) the presence of a group of signs suggestive of the disease; (ii) the typical histological appearance of biopsy material; (iii) the chronic and relatively asymptomatic course of the disease; (iv) the difficulty in demonstrating the tubercle bacillus by any method; (v) the absence of tuberculin sensitivity, which may change during the course of the disease.

Observations on the Thirty Cases.

In the majority of cases the age at which the disease was first recognized was between twenty-five and thirty-five years—17 of the cases falling into this group. The youngest patient seen was seventeen years of age when her illness became manifest. In Victoria the disease must be rare at earlier ages, for there are no cases recorded at the Children's Hospital, Melbourne, where the upper age limit is fourteen years. In a group of six the first overt manifestations appeared between the ages of fifty and sixty years.

The disease was found to be equally distributed between the sexes. The personality, bodily habitus and colouring varied widely. In southern Australia little assessment of ethnological factors is possible, as there are few aborigines and the population is predominantly of British and north-western European stock, although in recent years migrants from other European countries are becoming more numerous. With the exception of two Middle Europeans, who had the disease before entering Australia, all our patients were of Anglo-Saxon descent. A full review of occupations, past and present, was made, and no common factor was discovered.

In all cases the family history was traced back for as far as was possible and the patients were questioned regarding contacts with tuberculosis. Ten had had definite contact with tuberculous relatives and two were nurses who had cared for such patients.

In a study of past and associated diseases 12 patients were found to have a history of pneumonia and one of a torula abscess. Two are diabetics. Two patients, and one who is clinically regarded as suffering from sarcoidosis, have had *erythema nodosum* during the course of their illness. In one case (Case 69) this occurred at the onset of the patient's illness and was associated with lymph-node enlargement and pulmonary infiltration. In Case 67 and in the clinical case (Case 43) it drew attention to skin lesions that were already present. In both, enlarged lymph nodes were present and, in the latter, pulmonary infiltration.

The duration of the disease in our cases has varied widely. In several it extended over a period of twenty years, while in others the condition appeared to clear clinically within a few months. The duration of individual lesions also varied widely and often independently of that of the disease as a whole.

It will be observed on reference to Table I that there seems to be a predilection for certain organs, such as the lung, lymph nodes, skin and eye. These, however, are parts that can be readily observed and investigated, and there is no evidence to suggest that other less accessible sites are not involved with equal frequency. In three cases barely palpable lymph nodes were obtained that showed the typical histological changes; in another a lung that had cleared radiologically, after having been extensively involved several years previously, still showed histological evidence of the disease; and in a case in which the patient came to autopsy extensive visceral involvement was found that had not been recognized during life.

As a tissue or organ may be involved with little apparent functional disturbance or alteration in appearance, and as one set of local lesions may wax and wane independently of lesions elsewhere, it is clear that it is impossible to assess the extent of visceral involvement and the state of activity of the disease as a whole from the behaviour in those tissues that can be observed and investigated.

Although a study of Table I will show that evidence of a generalized disease was found in all 30 cases, the features seen are dealt with below according to the symptoms, the anatomical distribution of the lesions and the results of the laboratory investigations.

Symptoms.

Symptoms attributable to sarcoidosis were complained of by 25 patients and were the first evidence of illness in 17 cases. The symptoms were usually of a general nature, such as malaise, anorexia, loss of weight, tiredness, dyspnœa, night sweats and feverishness. Cough, when present, was non-productive unless there was a superadded infection. Such symptoms were most commonly complained of by patients with pulmonary involvement and were present only in the first months of the clinical course of the disease. Later they disappeared, despite persistence of widespread radiological changes. In most cases the symptoms were much less than would have been expected from the extent of these changes, in some being little

TABLE I.

Case Number and Initials of Patient.	Age. (Years.)	Sex.	Known Contacts with Tuberculosis.	Presenting Features.	General Symptoms and Signs.	Year of Observation.	Local Lesions.													
							Lymph Node Enlargement.													
							Cervical.	Axillary.	Epitrochlear.	Inguinal.	Mediastinal (X-ray Finding).	Skin Lesions.	Hepatic Enlargement.	Splenic Enlargement.	Ocular Lesions.	Lung Involvement. (X-ray Finding.)	Phalangeal Involvement. (X-ray Finding.)	Mucosal Thickening in Antra.	Confirmation Biopsies.
1 (R.S.)	56	F.	–	1946: enlarged inguinal lymph nodes.		1945	–	–	–	–	–	–	–	–	–	–	–		
						1947	+	+	–	+	–	–	+	–	–	–	–		Lymph node.
						1949	–	–	–	–	–	–	–	–	–	–			
3 (A.G.)	32	F.	+	1945: enlarged cervical lymph nodes.	1945: loss of weight; recurrent respiratory infections.	1945	++	–	–	–	++	–	–	–	–	–	–		Lymph node.
						1946	+	–	–	–	+	–	–	–	–	+	–	++	
						1947	+	–	–	–	+	–	–	–	–	+	–	++	Antrum.
						1948	+	–	–	–	–	–	–	–	–	–			
						1949	–	–	–	–	–	–	–	–	–	–			
						1950	–	–	–	–	–	–	–	–	–	–			
4 (B.M.)	19	F.	–	1947: findings at routine X-ray examination of chest.		1947	+	–	–	+	++	–	–	–	–	++	–		Lymph node.
						1948	–	–	–	–	+	–	–	–	–	+		–	
						1949	–	–	–	–	–	–	–	–	–	+			
						1950	–	–	–	–	–	–	–	–	–	–			
5 (L.A.)	55	F.	+	1944: skin lesions.	1944: cough, loss of weight, general malaise.	1944	–	–	–	+	+	++	–	–	–	++	+	–	
						1945					–	+++			–	+++			
						1946	–	–	–	–	–	++	–	–	–	++	+		Skin.
						1947	–	–	–	–	–	–	–	–	–	+			
						1948	–	–	–	–	–	–	–	–	–	+	+		
						1949	–	–	–	–	–	–	–	–	–	+			
						1950	–	–	–	–	–	–	–	–	–	–		+	
7 (C.McD.)	56	F.	+	1932: skin lesions.	1939: general malaise, cough, dyspnœa.	1932						++							
						1943						+++					++		
						1945	–	–	–	–	+	++++	–	–	–	–	+++		
						1946	–	–	–	–	+	+++++	–	–	++	++	++++		
						1947	+	–	+	–	+	+++++	–	–	++	+++	++++		Skin.
						1948	+	–	–	–	+	++++	+	–	+	+ +	++	–	Lymph node.
						1949	+	–	–	–	–	++	–	+	+	+	+		
8 (M.M.)	60	F.	–	1946: enlarged inguinal lymph nodes.	1946: cough, loss of weight, tiredness.	1946	++	+	++	++	+	–	–	–	–	+			Lymph node.
						1947	+	–	–	+	+	–	–	–	–	++			
						1948	–	–	–	–	–	–	–	–	–	++	–	+	
						1949	–	–	–	–	–	–	–	–	–	++			
10 (M.K.)	55	F.	–	1938: enlarged cervical lymph nodes.	1938: loss of weight, fever, malaise, anorexia.	1938	++	+	–	–								+	Lymph node.
						1939	++	++	–	–			–	–	–				
						1941	–	+	–	–									
						1942	–	–	–	–	–	–				–			
						1945	+	+	–	+	–	–			–	–	–	+	Lymph node.
						1946	+	+	–	+	–	–	–	–	–	–			
						1947	–	–	–	+	–	–	–	–	–	–	–	+	Lymph node.
						1949	–	–	–	–	–	–	–	–	–	–	–	+	
12 (R.L.)	46	M.	–	1941: skin lesions.	1943: loss of weight, slight malaise, bilateral facial palsy.	1941						+							
						1943	–	++	++	+	+	+	–	–	+++	+++	–	+	Lymph node.
						1945	–	–	–	–	+	–	–	–	+++	+			
						1947	–	–	–	–	–	–	–	–	++	+		+	
						1949	–	–	–	–	–	–	–	–	++	–			
						1950	–	–	–	–	–	–	–	–	++	–	–		
13 (G.C.)	56	F.	+	1922: malaise, fever.	Malaise, loss of weight; recurrent pyrexial attacks since 1922.	1922					++					+++			
						1938	++	+	–	+	–	–	–	–		–		++	
						1939	+	+	–	+		–			–				
						1940	++	++	+	+	+	–	–	–	–	–		+++	
						1941	++	++	+	++	–	+	–	–	–	–	–	++	Skin.
						1942	+	+	–	–		++			–				Lymph node.
						1943	–	–	–	–	–	+++	–	–	–	–			
						1947	–	–	–	–	–	++	–	–	–	–	–	++	Nasal mucosa.
						1949	–	–	–	–	–	++	–	–	–	–	–		Skin.
						1950	+	+	–	–	–	+	–	–	–	–		++	

TABLE I.—*Continued.*

Case Number and Initials of Patient.	Age. (Years.)	Sex.	Known Contacts with Tuberculosis.	Presenting Features.	General Symptoms and Signs.	Year of Observation.	Local Lesions.													Confirmation Biopsies.
							Lymph Node Enlargement.					Skin Lesions.	Hepatic Enlargement.	Splenic Enlargement.	Ocular Lesions.	Lung Involvement. (X-ray Finding.)	Phalangeal Involvement. (X-ray Finding.)	Mucosal Thickening in Antra.	
							Cervical.	Axillary.	Epitrochlear.	Inguinal.	Mediastinal (X-ray Finding).								
14 (W.W.)	55	M.	+	1944: enlarged cervical lymph nodes.	1944–1945: dyspnœa and loss of weight.	1945	+	+	–	–	++	–	–	–	–	+++		–	Lymph node.
						1946	+	–	–	–	+	–	–	–	–	++			
						1947	–	–	–	–	+	–	–	–	–	+	–	–	
						1948	–	–	–	–	–	–	–	–	–	–			
						1949	–	–	–	–	–	–	–	–	–	–	–	–	
18 (S.B.)	34	M.	+	1941: generalized lymph node enlargement.	1941: general malaise.	1941	+++	+++	+++	+++	–	–	–	–	–	+	–		Lymph node.
						1942	++	+	++	++		–			–	++		++	
						1945	+	+	+	+		–			+				Tonsil.
						1946	+	+	+	+		–			+	++			
						1947	+	+	+	+	–	–	–	–	+	++	+	+	Lymph node.
						1948	+	+	–	+	–	–	–	–	+	++	+	+	
20 (D.N.)	40	F.	–	1940: cough, loss of weight, generalized lymph node enlargement.	1940: cough, loss of weight.	1940	++	+	+	++	+	–	–	–	–	+++			Lymph node.
						1941	–	–	–	–	–	–	+	+	–	–			
						1946	–	–	–	–	–	–	–	–	–	–			Lung.
						1947	–	–	–	–	–	–	–	–	–	–	–	–	
						1948	–	–	–	–	–	–	–	–	–	–		–	
						1949	–	–	–	–	–	–	–	–	–	–			
21 (F.E.)	40	M.	–	1945: enlarged cervical lymph nodes.	1945: loss of weight, dyspnœa.	1945	++					+							Skin.
						1946	++	–	–	–	–	++			–	–	+		
						1947	+	+	–	+	–	+++	+	+	–	–			
25 (M.S.)	53	F.	–	1930: skin lesions.	Nil until final illness.	1930						+							Larynx. Skin. Lymph node.
						1945	–	–	–	–	+	+			–	+			
						1946						+			–	+			
						1947	+	–	–	–	++	+	–	–	–	+	–	++	
						1948	–	–	–	–	+	+	–	–	–	+		++	
						1949	–	–	–	–	+	–	–	–	–	–	–		
26 (P.R.)	24	F.	–	1947: enlarged lymph nodes.	1947: loss of weight, tiredness, loss of energy.	1947	++	++	–	+	++	–	–	–	–	+++	–		Lymph node.
						1948	+	+	–	–		–	–	–	–				
						1949	–	–	–	–	–	–	–	–	–	–			
27 (L.C.)	61	M.	–	1947: enlarged lymph nodes.	Malaise, fever, night sweats, cough, dyspnœa.	1940	–	–	–	–		–	–	–	–				Lymph node.
						1947	+	–	–	–	–	–	+++	+	–	+	–		
						1948	+	+	–	–	–	–	–	–	–	+			
						1949	+	–	–	–	–	–	–	+	–	+			
28 (J.Q.)	27	F.	+	1947: enlarged cervical lymph nodes.		1947	++	+	+	+	–	–	–	–	–	–			Lymph node.
						1948	–	–	–	–	–	–	–	–	–	–			
						1950	–	–	–	–	–	–	–	–	–	–			
32 (A.B.)	35	M.	–	1940: enlarged inguinal lymph nodes.	1940: fever with dyspnœa, malaise, anorexia, loss of weight.	1940	–	–	–	++		–	–	–	–				Lymph node.
						1941	–	+	+	++	++	–	–	–	–	+++	+		
						1942	+	++	++	++	++	–	–	–	–	+++		–	
						1948	–	–	–	–	–	–	–	–	–	+	–		
						1950	–	–	–	–	–	–	–	–	–	+			
35 (V.C.)	32	F.	+	1948: pyrexia.	1948: pyrexia.	1948	+	–	–	+	–	–	–	–	–	+++	–		Lymph node.
37 (K.W.)	59	F.	–	1948: enlarged cervical lymph nodes.		1947	+	–	–	–		–			–				Lymph node.
						1948	+	–	–	–	–	–	+	–	–	–	–	–	
44 (J.S.)	21	F.	–	1948: general symptoms.	1948: general malaise, loss of weight, pyrexia.	1948	+	+	–	–	++	–	–	–	–	++	–	–	Liver biopsy. Lymph node.
						1949	+	+	–	–	+++	–	+	++	–	+			
45 (L.M.)	34	F.	+	1947: skin lesion.		1945					–	–			–	–			Skin. Lymph node.
						1948	+	–	–	+	–	+	–	–	–	–	–	–	
						1949	+	–	–	–	–	+	–	–	–	–			
						1950	+	–	–	–	–	+	–	–	–	–			

TABLE I.—*Continued.*

Case Number and Initials of Patient.	Age. (Years.)	Sex.	Known Contacts with Tuberculosis.	Presenting Features.	General Symptoms and Signs.	Year of Observation.	Lymph Node Enlargement.						Local Lesions.								Confirmation Biopsies.
							Cervical.	Axillary.	Epitrochlear.	Inguinal.	Mediastinal (X-ray Finding).	Skin Lesions.	Hepatic Enlargement.	Splenic Enlargement.	Ocular Lesions.	Lung Involvement. (X-ray Finding.)	Phalangeal Involvement. (X-ray Finding.)	Mucosal Thickening in Antra.			
54 (V.S.)	30	F.	—	1948 : general malaise.	1948 : general malaise.	1948 1949 1950	—	—	—	—	—	—	—	—	—	+	—	—			Lymph node.
59 (E.B.)	37	M.	—	1946 : skin lesions.		1946 1947 1949 1950	+	+	+	+	+	+	+	—	—	+	—	+			Lymph node.
60 (A.D.)	53	M.	—	1925 : skin lesions.		1925 1948 1949	—	—	—	—	—	+	+	—	—	+	—	—			Skin.
66 (E.G.)	39	M.	—	1935 : enlarged lymph nodes.		1935 1940 1944 1947 1948 1949	+	+	—	+	+	—	—	—	—	—	—	—			Lymph node.
67 (J.M.)	81	M.	+	Skin lesion prior to 1949.	1949 : loss of weight, fever, malaise, cough, dyspnœa, arthralgia, *erythema nodosum*.	1949	+	+	+	+	+	+	+	+	—	—	—	—			Skin.
68 (H.S.)	61	M.	+	1948 : skin lesions.		1946 1949 1950	—	++	—	—	—	—	++	—	—	—	—	+			Skin.
69 (R.P.)	23	F.	+	1949 : *erythema nodosum*.	1949 : *erythema nodosum* with general symptoms.	1949 1950	++	—	—	—	—	—	—	—	—	++	—	—			Lymph node.
75 (C.H.)	27	M.	—	1949 : eye lesions.	General malaise, loss of weight, facial palsy (bilateral).	1949	—	—	—	—	++ ++	—	—	—	++ ++	—	—	—			Liver.

more than a slight malaise. Five patients, however, lost over one stone in weight within six months, and the symptoms were severe enough to cause five to seek their first medical advice. Besides occurring in cases with pulmonary involvement, these symptoms were present during the enlargement of lymph nodes in one case and during the development of extensive skin lesions in another.

Symptoms referable to local lesions were encountered only where the eye, upper part of the respiratory tract and lymph nodes were involved. Those associated with eye lesions were of iridocyclitis and will be dealt with elsewhere. In the upper part of the respiratory tract they were indistinguishable from those found in non-specific infections. Discomfort from enlarged lymph nodes was complained of by three patients.

Anatomical Distribution.

Lymph Nodes.

Enlargement of superficial lymph nodes was observed in 27 cases, and of mediastinal nodes in 18, in one of which no superficial nodes were palpable. Besides being the most common lesion, this was the most frequent presenting feature, as it occurred in 13 cases. In two of these this has been the only evidence of the disease. In two others the only other sign was a slightly enlarged liver, on which no biopsy was carried out. In six others the patients were found to have associated pulmonary lesions, while in the remaining three, lesions subsequently developed elsewhere.

The nodes varied in size from 0·5 to 2·0 centimetres in diameter (Figure VIII). They were discrete, firm on palpation and, in all except three, painless. They resembled those found in Hodgkin's disease, although in some cases they were of softer consistency.

The length of time during which nodes were palpable varied widely, but they usually became impalpable during the course of the disease. In Case 25 an impalpable node, removed from the neck nineteen years after the first sign of the disease, revealed the typical changes on histological examination. It is evident that while a node or a group of nodes may become impalpable during the course of the disease, they may still remain the site of the disease process.

Skin.

Skin lesions were present in 11 cases. As they were the first evidence of sarcoidosis in nine of these, they were the second most common presenting sign. In no case was the skin the only organ affected.

The skin lesions appeared to be far more chronic than those found elsewhere. In three cases they have been present for twenty years and, so far as can be ascertained, some of the lesions are still in the original sites, although newer skin lesions have developed elsewhere. In some a new lesion appeared while an old one disappeared with or without the formation of a visible atrophic scar. Such scars were seen in Case 5 and Case 21, while none was apparent in Case 13 (Figures VI and VII). The involvement of the skin is not always of long duration; thus in Case 5 sarcoids were present for only two years. All forms of cutaneous sarcoidosis were much more commonly seen on the upper half of the body. Lesions of the skin over the abdomen were not observed, but they were present in the skin of the legs in three cases, and in one of these the soles of the feet were affected. In none was there pain or pruritus, and the only complaint was of disfigurement from lesions of the face and hands.

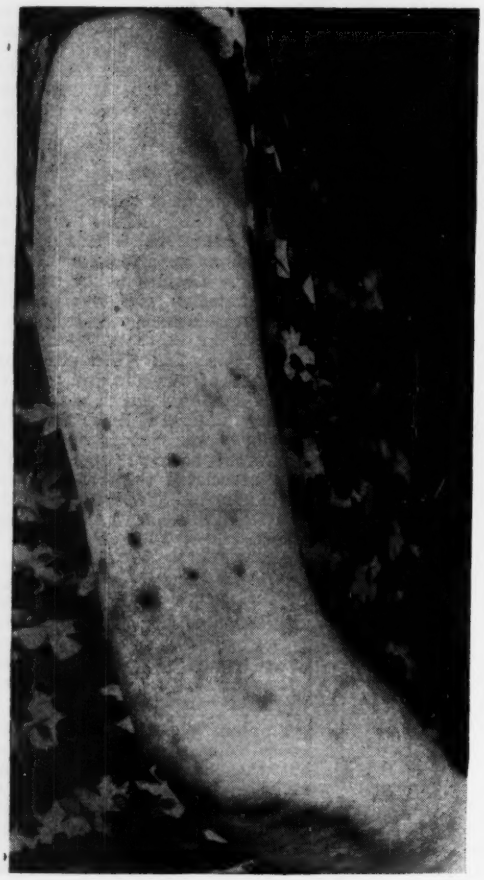

Figure VI.

Case 13. Distribution of sarcoids on patient's right upper arm on October 17, 1947.

In two cases (Cases 59 and 67) sarcoids have developed in the site of a previous injury, which in both had occurred many years before (Figure VIII). In no case has ulceration followed the removal of a small piece of material for biopsy, and healing has been prompt in all.

The three forms seen were Boeck's sarcoid, Besnier's *lupus pernio* and the subcutaneous sarcoid of Darier and Roussy. The difference between the sarcoid and the *lupus pernio* is that the former is a discrete asymmetrical lesion, while the latter merges with the surrounding skin and is usually symmetrically distributed.

The sarcoids varied greatly in size—from small nodules less than one centimetre across to large areas of over ten centimetres in diameter. The colour appeared to vary with the thickness of the plaque and its situation in the skin. In two patients with very superficial lesions of little apparent depth they were pinkish-red, scarcely darker than the surrounding skin. Those penetrating more deeply into the dermis were of purplish colour. Most were roughly circular in shape, firm in consistence, and slightly elevated. In the more superficial plaques the border was raised, giving the impression of a "growing edge", while the depressed central area was covered by a fine desquamation (Figures IX and X). No follicles were seen in any of these sarcoids, and in only one were there visible superficial vessels. In Case 68 the patient had a variant of the above. The lesions on his legs and elbows were flat, pale-purple areas of normal texture, with a serpiginous border (Figure XI).

Figure VII.

Case 13. Distribution of sarcoids on the same arm as shown in Figure VI on September 3, 1948.

Lupus pernio was seen in two cases (Cases 7 and 13); in both, other forms of cutaneous sarcoidosis were also present. The sites included the cheeks, ears, nose, fingers and toes, where it formed large, swollen, symmetrical patches of soft infiltration with margins that merged imperceptibly with the surrounding normal skin. The colour varied from dark purple to pink. The skin over these areas was thin and in some places shiny, and the finger and toe nails in one case were longitudinally furrowed and irregular (Figure XII). In both cases the hands were affected, but functional disability was slight and ordinary duties were readily performed. The degree of swelling and coloration was lessened by warmth and rest. In Case 7 the changes were very gross, resulting in large, pale-purple, swollen, pendulous cheeks and swollen fingers and toes where the *lupus pernio* was associated with rarefying changes in the phalanges (Figures XII, XIII and XIV). In Case 13 the swelling of the fingers was uniform and pink in colour and resembled chilblains; there were no bony changes. In this patient *lupus pernio* was also present over the tip of the nose and merged with nasal mucosa known to be affected by the disease (Figure XV).

The subcutaneous sarcoids of Darier and Roussy were seen only in Case 7, in which numbers were present in the subcutaneous fatty tissue of the arms (Figure XII). They consisted of roughly spherical soft masses of up to four centimetres in diameter, composed of aggregations of small, purple, sago-like granules, which could be seen more readily if a glass slide was pressed on the overlying skin (Figure XVI).

Lung.

There were radiological signs of pulmonary involvement in 21 cases and of hilar or mediastinal lymph node enlargement in 18. On this evidence the lungs were the second most frequent site of the disease. Only one of these cases was discovered as the result of a routine X-ray examination.

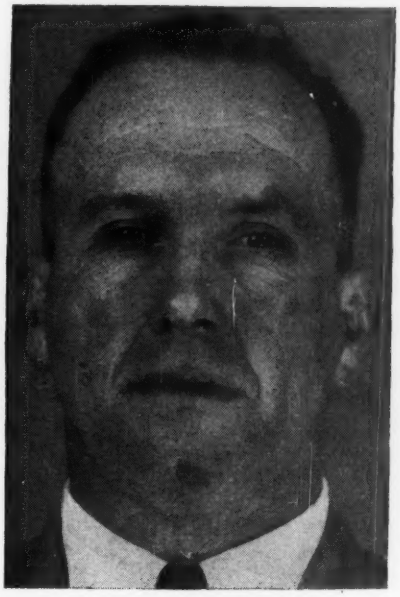

FIGURE VIII.

Case 59. Sarcoid formation in scars associated with enlarged preauricular lymph nodes.

The radiological appearance varied from a few ill-defined scattered linear markings to a dense nodular infiltration occupying portion of, or the whole of, one or both lung fields. In serial X-ray films a variety of changes was seen. The shadows were observed to increase in density, to show little change over long periods, or to diminish partly or completely except for a slight residual increase in pulmonary markings (Figures XVII and XVIII). In some the enlargement of the hilar lymph nodes preceded the infiltration but subsided as the latter increased. However, in other cases one or the other appeared to be the only change present.

Even in the presence of extensive pulmonary involvement physical signs were absent or few and non-specific, although symptoms attributable to sarcoidosis occurred frequently in the early months of the clinical course of the disease, to disappear despite the continued widespread X-ray changes. These symptoms were usually of a general nature. Cough, when present, was non-productive, unless sinusitis was also present. Patients with these symptoms were at first regarded as being possibly tuberculous, a view which the X-ray examination seemed to confirm, but no acid-fast bacillus was ever found and the result of a Mantoux test was negative in all.

More important than the disappearance of symptoms in the continued presence of X-ray evidence of pulmonary changes is the presence of histological evidence of pulmonary lesions, when the X-ray picture appeared to have become normal. In Case 20 extensive X-ray changes had been present; seven years later a biopsy of lung, taken during the removal of pulmonary hydatid cysts, showed sarcoid follicles, despite the fact that X-ray pictures taken at this time showed no changes suggestive of sarcoidosis (Figures XIX and XX).

Hæmoptysis occurred in three cases. In Cases 27 and 66 this happened during an illness that appeared to be pneumonia on clinical and radiological grounds, while in Case 60 the patient has had typical skin lesions for many years and a negative result from the Mantoux test, but was known to have X-ray signs of apical fibrosis at the time the hæmoptysis occurred.

FIGURE IX.

Case 45. Boeck's sarcoid with raised margin and desquamating centre.

Upper Part of the Respiratory Tract.

Proved lesions of the upper part of the respiratory tract were found in four of our patients. When it became apparent that this was a relatively common site, all patients with any suggestion of disease of the upper part of the respiratory tract were referred to an oto-rhino-laryngologist.

The lesions found involved the tonsils, the mucosa of the nose and accessory sinuses, and the larynx, and could not be distinguished clinically from those of non-specific inflammation. None of the sago-like nodules described in the literature were seen. Operative treatment was undertaken only on general grounds, except when biopsies were taken from the inferior turbinate bone.

Tonsils.

Chronically infected tonsils which showed sarcoidosis on section were removed from one patient (Case 18), who also had sinusitis. One other patient (Case 27) has refused operation for similar tonsillitis. Tonsils were not removed from other patients because many of the patients had had tonsillectomy earlier in life and because no tonsil was removed for purely diagnostic purposes.

Nose and Accessory Sinuses.

The nose and its accessory sinuses were involved in inflammatory changes in six cases. In two of these sarcoidosis of the mucosa has been seen on section. In Case 3

the patient has had chronic purulent sinusitis for several years and has obtained relief from antrostomy. In Case 13 the patient has had much operative treatment for chronic sinusitis of many years' duration, and at present she has gross atrophic rhinitis with much crusting and a perforated septum. Recently the changes in the mucosa have become confluent with *lupus pernio* of the skin around the nostrils (Figure XV).

There is a history of an antrostomy in three other cases, but at the time of operation no material was examined. In Case 10 the patient has a long history of sinusitis; she had a bilateral antrostomy in 1938 and has now atrophic rhinitis; a biopsy of the inferior turbinate bone in 1949 showed chronic inflammatory changes only. In Case 18, in which sarcoidosis of the tonsils was found, there was also sinusitis that responded to conservative measures, and in Case 68 there is mild atrophic rhinitis.

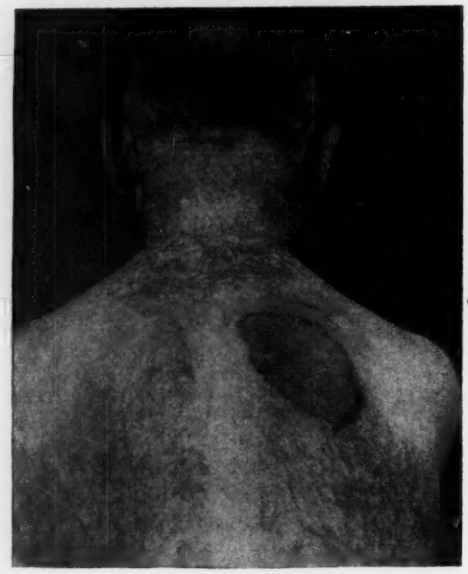

FIGURE X.
Case 60. Boeck's sarcoid showing raised margin.

It will be seen that three patients have atrophic rhinitis. It is possible that this is a sequel to florid sarcoidosis.

Larynx.

Sarcoidosis of the larynx is rare. One of our patients (Case 25) developed this manifestation. The whole larynx became involved in a condition of gross œdema, and later, after X-ray therapy, became fibrosed and distorted. The œdema reappeared, and fibrous stenosis of the œsophagus that required dilatation developed at the post-cricoid level.

Eyes.

The eyes in all cases were examined by ordinary clinical methods, and 23 patients were referred to an ophthalmologist, who found that six had ocular lesions attributable to sarcoidosis. In an unproven case (Case 24), not included in the main series because no biopsy material has been obtainable, the patient also has eye lesions; as she is considered clinically to be suffering from sarcoidosis, her case is included with those discussed in the contribution by Dr. Nancy Lewis.

Although no fully developed case of Heerfordt's syndrome was found, the patients in Cases 12 and 75 (Figure XXI) had bilateral facial palsy in conjunction with ocular lesions. Neither had swelling of the salivary or lachrymal glands.

Bone.

Radiological changes in the phalanges were seen in a well-developed degree in Case 7, in which they were associated with gross *lupus pernio* of the overlying skin (Figures XII, XIV). Similar bony lesions, though of much less degree and without overlying *lupus pernio*, were seen in four other cases.

In spite of the fact that special attention was paid to bones in the routine X-ray examination of the chest and sinuses, and although other bones were submitted to X-ray examination from time to time, the phalanges were the only ones in which suggestive changes were found.

Liver.

In 11 cases the liver was palpable at one time during the course of observation; in nine it could be felt only on full inspiration. In Case 27 no record was made of any hepatic enlargement during a period in hospital in 1940, but in October, 1947, the liver extended ten centimetres below the right costal margin. At this stage the results of a liver biopsy and liver function tests were normal. By April, 1948, the liver had become impalpable and has remained so since. No explanation for these observations can be submitted.

FIGURE XI.
Case 68. Boeck's sarcoids on the right leg.

Liver biopsies were carried out in three other cases, with positive results in two, although in neither of these was the liver palpable.

Spleen.

The spleen was palpable in six cases. In none was the enlargement gross.

Alimentary Canal.

Evidence of involvement of the alimentary canal was found only in Case 25, in which a post-cricoid stricture of the œsophagus was seen in association with sarcoidosis of the larynx.

Cardio-Vascular System.

No evidence has been found of involvement of the tissues of the heart or of *cor pulmonale* from extensive pulmonary lesions.

Electrocardiograms were prepared in nine cases, and in eight cases of possible sarcoidosis with extensive pulmonary lesions. In none of these was any change present that could not be explained by the patient's habitus or

hypertension. The leads used were I, II, III, IIIb, AVL, AVF, V1, V2, V3, V4 and V5.

Laboratory Investigations.

Hæmatological Findings.

Routine blood counts were carried out in 25 cases. There has been no significant degree of anæmia in any. In two cases (Cases 12 and 14) the hæmoglobin value was over 140% and red cell counts were over 6,500,000 per cubic millimetre during a phase when the lung was extensively involved. At a later stage when the lung lesion had regressed the polycythæmia diminished.

In nine cases the total white cell count was at the lower limits of normal (4000 to 5000 cells per cubic millimetre), and this was associated with a neutrophile polymorphonuclear leucocyte count of below 3000 cells per cubic millimetre and usually with a lymphocyte count of below 1500 cells per cubic millimetre; but irrespective of the total leucocyte count there was a significant increase in circulating old metamyelocytes in 15 cases, in which over 500 cells per cubic millimetre were present. In 13 cases a monocytosis was found of over 500 cells per cubic millimetre, and in nine there was a lymphocytopenia with readings below 1200 cells per cubic millimetre. An eosinophilia of over 500 cells per cubic millimetre was observed in three cases; in one of these this was associated with hydatid cysts in the lung, and after removal of these it was no longer present. There was no consistent association between the changes in the counts of the various leucocytes, and no correlation could be drawn between the hæmatological findings and either the extent or the duration of the demonstrable lesions.

FIGURE XII.

Case 7. Subcutaneous sarcoids of Darier and Roussy in the arms, *lupus pernio* of the fingers and deformity of the nails.

Serum Proteins.

In 27 cases determinations of the serum albumin and globulin content have been made. There has been an elevation of the total serum protein content above eight grammes *per centum* in 10 of these, accounted for by an increase in globulin content in eight cases, whereas in two the increase has been in serum albumin content without any hyperglobulinæmia. In a further six cases there was an increase in serum globulin content at the expense of the serum albumin content, and in some of such extent as to invert the albumin-globulin ratio. In the remaining 11 cases the serum proteins were within normal limits.

The changes in serum protein content could not be related to the hæmatological findings. They have not always been present in cases with widespread lesions and have occurred in cases without demonstrable lesions.

Tuberculin Sensitivity.

In this series tuberculin tests were carried out in all cases and in the majority with old tuberculin in 1:1000 dilution, derived from human, bovine and avian strains. Tests with higher strengths have been made with human tuberculin only (Table II). No patient has reacted to an avian strain.

FIGURE XIII.

Case 7. *Lupus pernio* of both cheeks with telangiectatic vessels, crusting and cutaneous horns.

With most of the patients these tests have been repeated, and three developed a positive reaction to 1:1000 dilution of old tuberculin during the period of observation (Cases 3, 5 and 45); one patient developed a positive reaction to a dilution of 1:100 (Case 25). By the time the change in tuberculin sensitivity occurred, the patients in Cases 3 and 5 had no lesions demonstrable by clinical methods, while in Case 45 skin lesions were extending and in Case 25 the patient became tuberculin-sensitive during the terminal phases of her disease.

Sundry Investigations.

The erythrocyte sedimentation rate (Cutler) was measured in 26 cases. In 20 of these diagonal curves were obtained with indices ranging from 12 to 30. In the remaining six cases there were horizontal curves and

normal indices; the six patients still had demonstrable lesions.

The results of the Wassermann and Kahn tests were negative in all cases. Skin sensitivity to coccidioidin was tested in 21 cases and to histoplasmin in five, but no reaction was observed in any.

Estimations of the levels of serum calcium and alkaline phosphatase and of blood cholesterol were made in 15 cases. The results were within normal limits in all except Case 1, in which the serum calcium content was 14 milligrammes *per centum*. In this case the serum phosphate content was 3·4 milligrammes *per centum*.

Bacteriological Investigations.

Attempts were made to demonstrate the tubercle bacillus in sputum and gastric content in 17 cases. Tests were repeated on many occasions, and in all the results were negative (Table III).

FIGURE XV.

Case 13. *Lupus pernio* of the nose, which is confluent with changes in the nasal mucosa. There is a fading sarcoid on the forehead above the inner end of the left eyebrow.

In many cases affected lymph nodes or skin lesions obtained at biopsy were reduced to an emulsion and inoculated into experimental animals in duplicate, or an attempt was made to grow a culture of an organism (Table IV).

In four cases (Cases 7, 8, 10 and 26) after eight weeks the spleens and lymph nodes of the guinea-pigs inoculated were ground and injected into a second batch.

All guinea-pigs inoculated were given one millilitre of old tuberculin (undiluted) after eight weeks, to exclude the possibility of a mycobacterial infection of low pathogenicity for guinea-pigs which might have led to the development of tuberculin sensitivity. None of these investigations has given a positive result.

In one case (Case 25), human tubercle bacilli were recovered from a guinea-pig inoculated with abdominal lymph nodes obtained at autopsy, whereas the results of previous attempts with a lymph node excised during life had been negative.

All biopsy material was stained by Ziehl-Neelsen technique, and no acid-fast bacillus was seen in any section showing the sarcoid reaction. In Case 7 an abdominal lymph node, removed during a cholecystectomy in 1945, showed acid-fast bacilli in a caseating lesion of the structure seen in tuberculosis.

Attempts were made to isolate a virus from suspensions of biopsy material (a lymph node in Case 26 and skin lesions in Cases 7 and 10). Dr. Frank Fenner, at the Walter and Eliza Hall Institute of Medical Research, carried out the experiments, which consisted of the inoculation of the suspensions, undiluted and diluted 1:100, into the yolk sac of seven-day-old chick embryos and on to the chorio-allantoic membrane of eleven-day-old chick embryos and of intranasal and intracerebral inoculation in mice. In each instance one blind passage was made, but the results of all the experiments were negative.

FIGURE XXI.

Case 75. Bilateral facial palsy.

Treatment.

In these cases a number of different forms of treatment were given both before and after the beginning of this survey, but as no controlled investigation was carried out and as the disease is characterized by remissions, it is impossible to do more than state the results.

Nine patients received X-ray therapy. In three, enlarged lymph nodes subsided during treatment. Skin lesions were irradiated in five; they became less conspicuous in two, in two no alteration could be seen, and in one the condition progressed. Several had X-ray therapy to the chest. In one of these (Case 12) this was given for tumours that ultimately proved to be hydatid cysts. On their removal at operation fourteen months later, both lung and pleura showed sarcoidosis on section. One patient with gross involvement of the sinuses was treated, with relief of pain, but no other evidence of improvement. A patient with laryngeal stenosis was temporarily benefited.

Calciferol was given orally in doses of from 30,000 to 100,000 units a day over a period of months to eight patients. Local improvement was noted during this treatment in three cases of cutaneous involvement and in one of ocular involvement. It was given to one patient (Case 25) who later died. When the higher doses were used, monthly estimations of serum calcium content were made.

Streptomycin, in a month's course of 0·5 to 1·0 gramme daily, was given in three cases without benefit.

Ultra-violet light, penicillin, arsenicals, "Bismol" and gold have been without effect when used in isolated cases.

Warmth and rest were repeatedly observed to be of temporary value in causing the more severe dermatological lesions to become smaller and paler, and treatment, often surgical, was necessary for involvement of the eyes and upper part of the respiratory passages.

Differential Clinical Analysis of the Seventy-Five Cases in this Investigation.

Of the 75 cases considered in this investigation, four have been wholly excluded from consideration as insufficient data have been obtained to warrant their inclusion.

In 30 cases the diagnostic criteria set out in the beginning of this article were fulfilled. The clinical features of these have already been described.

Two patients were seen from whom no biopsy has been obtainable but who appear to have a sufficient number of characteristic lesions to warrant the making of a clinical diagnosis of sarcoidosis. These are the patients in Cases 24 (M.P.) and 43 (H.B.)

In Case 24 the patient (M.P.) is a single nurse, aged forty-eight years. She had pneumonia as a child. Her mother died of tuberculosis, and she has nursed tuberculous patients. A twin sister has no evidence of sarcoidosis and has a positive Mantoux reaction. Both have hypertension.

In 1939 an X-ray examination showed apical scarring of the right lung considered to be due to healed tuberculosis.

TABLE II.

Strength.	Number of Patients.	Positive Result.
1 : 1000 O.T.	30	2 (Cases 12, 27)
1 : 100 O.T.	12	1 (Case 13)
1 : 10 O.T.	6	—

In a further X-ray examination in November, 1945, no change was observed, but in October, 1946, there was enlargement of both hilar shadows, while in March, 1947, the hilar lymph nodes were sufficiently large for Hodgkin's disease or lymphosarcoma to be considered.

In October, 1946, she began to receive treatment for iritis, which was followed by chronic glaucoma. There was no facial palsy or parotitis.

She was first examined in this survey in August, 1947, when no abnormality was found apart from the iritis, the chest X-ray appearances and changes associated with her hypertension.

An X-ray examination in October, 1948, showed the glandular enlargement to be slightly less, but a fine mottling was now present throughout both lungs. She took calciferol (30,000 units daily) for the next twelve months, and in January, 1950, she looked and said that she felt greatly improved. Her eyesight was better, and an X-ray examination showed no glandular enlargement and a decrease in the mottling. The result of the Mantoux test has always been negative.

TABLE III.

Method of Examination.	Number of Cases.
Sputum smear	11
Sputum culture	8
Culture of fasting gastric content	8
Guinea-pig inoculation with gastric content and sputum ..	3
Guinea-pig inoculation with pleural fluid	1

In this case the only reasonable alternative diagnosis is frank tuberculosis, which appears unlikely from the clinical course of her disease.

In Case 43 the patient (H.B.) is aged thirty-one years. Her husband has sarcoidosis and is the patient (S.B.) in Case 18 of our series. Her past medical history is normal, and there has been no known contact with tuberculosis.

She was first examined by us in November, 1948, having been quite well until three months previously, when she developed *erythema nodosum* on the legs and to a lesser extent on the arms. A biopsy of one of these areas showed a non-specific infiltration with mononuclear cells and an occasional giant cell. In addition to these there were over her back a number of slightly raised, circular, reddish, discrete plaques of 1·0 to 1·5 centimetres in diameter, which appeared to be sarcoids. Several small lymph nodes were palpable in the superficial groups, as was the liver on full inspiration. X-ray examination of the chest showed a fairly fine close nodulation throughout both lungs, and the results of Mantoux tests were negative. It was not possible to secure further biopsy material.

Although these two cases have not been included in our main series, there seems no doubt that they are indeed cases of generalized sarcoidosis.

The patients in two cases—Cases 15 (J.M.) and 31 (J.E.)—whose condition at one period could not be distinguished from sarcoidosis, eventually developed frank tuberculosis. At an early stage of their disease lymph-node biopsy and pulmonary X-ray examination showed the findings seen in sarcoidosis. No tubercle bacilli could be recovered, and the results of Mantoux tests were negative. Later, in each a general deterioration occurred, the result of the Mantoux test became positive, tubercle bacilli were found, and signs of pulmonary tuberculosis developed. Both died, and at autopsy the findings were those of frank caseating tuberculosis.

TABLE IV.

Method.	Case Number.
Guinea-pig inoculation	7, 7, 8, 10, 13, 25, 26, 54, 59
Rabbit inoculation	7, 7, 8, 10, 13, 25, 26
Mouse inoculation	7, 13, 25
Rat inoculation	7, 13, 25
Dubos "Tween 80" Medium	7, 8, 10, 13
Lowenstein medium	7, 7, 8, 10, 13, 25, 45, 54, 59
Blood agar medium	7, 7, 8, 10, 13, 25, 45, 59
Sabouraud medium	7, 13, 25, 45

In three cases an isolated lymph node was removed that showed the non-caseating sarcoid reaction. In none was any other sign indicative of a generalized disease found, and they have been excluded from the main series on this account. All three patients proved to be tuberculin-sensitive and *Mycobacterium tuberculosis* was obtained from the lymph node of one by guinea-pig inoculation. Prolonged observation or further knowledge of these conditions will be necessary before the true nature of these lesions is known, but at present they are being regarded as those of non-caseating localized tuberculosis.

There remain three groups of cases. The first is of those in which sarcoidosis is the possible diagnosis, the second of those in which other diagnoses have been made, and the third is of as yet undiagnosed cases.

In the 15 cases forming the first of these groups, in which sarcoidosis is possible, sufficient evidence has not yet become available to allow the making of more than a tentative diagnosis. Eight were discovered on routine X-ray examination of the chest, and there were no other symptoms or signs referable to the disease. In five others the patients had complaints of a general nature, such as loss of weight, cough, dyspnœa and fever. In these also the chest X-ray findings were characteristic, although a lymph-node biopsy in three showed non-specific inflammatory changes, the tonsils in another showed no sarcoidosis, and in the remaining case there was associated chronic rheumatoid arthritis. The last two of the 15 possible cases showed some of the components of Heerfordt's syndrome. In one there were bilateral facial palsy, dysphagia and chorioiditis, and in the other bilateral parotitis and possible iritis.

Twelve cases in which the patients were found to be suffering from other conditions comprise the second group. Of six of the patients in this group presenting with enlarged lymph nodes, two were proved to have Hodgkin's disease, two had less common reticuloses, another with leuchæmia had sarcoid-like areas of infiltration in the skin and associated pulmonary tuberculosis, while the remaining patient had frank tuberculous adenitis. Four others were referred on account of a chest X-ray appearance that simulated that of sarcoidosis, but one was shown to have cystic disease of the lung, one pulmonary eosinophiliosis, one chronic pulmonary congestion from rheumatic carditis and the last suppurative pneumonitis. Another patient was referred with *erythema nodosum*, in whom X-ray examination showed an enlarged hilar gland with a zone of pulmonary infiltration above it. The Mantoux reaction was positive, and the patient is regarded as having a primary tuberculous complex. The remaining patient

in this group had a lump in the breast, which in some areas contained typical follicles. Further sections revealed a caseating tuberculous lesion.

The third group is of seven referred cases which remain diagnostic problems despite investigation. The evidence is not sufficient to include them in any of the previous groups.

Thus it will be seen that of the 75 patients examined, 30 are proved to have sarcoidosis, two have sarcoidosis on clinical grounds, five have a condition that cannot be distinguished adequately from tuberculosis, fifteen are possibly suffering from sarcoidosis, twelve have been proved to have some other condition, seven remain with an undiagnosed condition, and four have been entirely excluded from consideration.

Discussion.

The nature of the disease is that of a chronic infective process. The pattern of tissue reaction, with the formation of follicles of endothelioid cells and the subsequent course of resolution or fibrosis, is indistinguishable from that seen in many inflammatory conditions of known ætiology. This behaviour is reflected in the changes seen clinically, in which lesions, often of long standing, may resolve with or without the formation of scar tissue.

The clinical course of the disease is similarly that of a chronic inflammatory process. Where the development of extensive tissue involvement can be observed, this is frequently accompanied by general constitutional symptoms.

The inflammatory nature of the disease is further shown by the changes in the leucocyte counts and serum proteins. These are not characteristic, but are a non-specific effect such as is common in some subacute inflammatory conditions. These changes might be expected to occur during extension of the disease. That no evidence on this point is found in this series may be because many patients had the disease for different periods of time before coming under observation, and because of the inability to assess the changes in the internal viscera as a whole.

The distribution of the lesions can be most readily interpreted as being due to a hæmatogenous dissemination of the ætiological agent, and the sporadic appearance of new lesions suggests either the presence of a discharging focus of infection or the renewed introduction of the agent into the host.

Although the tubercle bacillus has been recovered but rarely from these lesions, most modern discussion centres around the relationship of this condition to tuberculosis. It is clear that in this paper little information has been presented to support the view that sarcoidosis is caused by the organism of tuberculosis, although some of our observations are significant in this respect.

Acid-fast bacilli were found in an abdominal lymph node in a case in which extensive and classical lesions of sarcoidosis are present, while in another tubercle bacilli were grown in culture from non-caseating lymph nodes obtained at autopsy. Two patients, not included in the main series, who at one time fulfilled all our criteria of diagnosis, died of tuberculosis. In no fewer than 11 other cases the patients knew of close contact with tuberculous patients. After this observation relatives of some were examined, and in one pulmonary tuberculosis was discovered. Clearly further investigation would be of value, for no such epidemiological survey has been reported. When the patients were first observed, the result of the Mantoux test was negative in all but two cases, and in these it was not carried out until at least two years after the first signs were observed. In neither is there now any sign of active sarcoidosis, and both patients are well. Thus a positive reaction was found in only 7% of cases at this stage. The incidence of positive reactors in this community is not known with certainty, but in non-medical students between the ages of twenty and twenty-three years at the University of Melbourne it is 36% (Lowe and Hallam, 1947), and in a group of individuals of the ages found in our cases it should be higher than 7%. The reaction became positive in four cases while the patients were under observation. Two of these patients now show no signs of either sarcoidosis or tuberculosis, one died of bronchopneumonia and at autopsy tubercle bacilli were recovered, and the remaining patient still has a skin sarcoid.

The difficulty in assessing the degree of involvement of organs that are not accessible to examination or investigation has been stressed. It follows that it is impossible to predict the course of the disease in any case, and difficult to form a concept of the natural history of the condition as a whole. The course in individual cases depends on a combination of factors—the variable duration, the remittent nature of the process and the possible sequelæ—and from the experience gained in this study may involve ostensibly complete resolution, with or without apparent scarring, continuance over an indefinite number of years or death from tuberculosis.

At the beginning of this paper various criteria for diagnosis were set down, and it is pertinent at this stage to review them in the light of our experience.

The first criterion referred to the presence of a group of signs suggestive of the disease. Sarcoidosis cannot be diagnosed in the absence of evidence of generalization, as an isolated lesion with a typical histological structure may be some other condition. In some cases a grouping of characteristic lesions will enable a reasonable clinical diagnosis to be made, but where the lesions are not suggestive of any of the classical manifestations, not even a tentative diagnosis will be possible.

The second criterion was the typical histological appearance of the biopsy material. As has been pointed out earlier, this appearance, although typical, is not specific and may occur in a number of other conditions, of which tuberculosis is the most common.

The third criterion was the chronic and relatively asymptomatic course of the disease. This is an overstatement. The disease in some cases appeared to be of short duration. In many others it caused obvious symptoms and disabilities of varying degrees of permanency. Death occurred in one case of sarcoidosis and in two other cases which at one time were considered to be of sarcoidosis.

During the progress of extensive tissue involvement general constitutional symptoms were frequent, although they were never as severe as might have been expected from the extent of the lesions. Thereafter the disease was virtually asymptomatic despite the persistence of the widespread tissue involvement. In addition to these general symptoms, symptoms directly attributable to involvement of the eye, larynx and nasal mucosa were recorded.

The fourth criterion referred to the difficulty in demonstrating the tubercle bacillus by any method. Acid-fast bacilli have been observed in only one patient during life. These were in an abdominal lymph node of a patient still clinically suffering from sarcoidosis, in whom the result of a Mantoux test is negative. In one case tubercle bacilli were grown from non-caseating lymph nodes obtained at autopsy.

The fifth criterion was an absence of tuberculin sensitivity. A negative result from a Mantoux test is of great help in arriving at a diagnosis of sarcoidosis, although a patient may have a positive reaction and yet show all the other features of the syndrome. A change in tuberculin sensitivity is usually associated with a change in the nature of the disease.

It will be obvious that each of these criteria has needed qualification, and we are left with a concept of a generalized disease having a typical histological pattern, that runs an asymptomatic course unless extensive tissue involvement is in progress, or unless an organ of small compass is affected.

With available diagnostic methods it is impossible to assess the extent of the process or its duration.

As no criterion is specific, the diagnosis must depend on the assessment of all the features present.

Regardless of ætiological considerations, the main clinical difficulty is to exclude some forms of tuberculosis.

Inability to obtain the tubercle bacillus does not do this, and in the present state of our knowledge it does not appear possible to state that the presence of the tubercle bacillus excludes sarcoidosis. This difficulty becomes more apparent from a consideration of the patients in whom frank tuberculosis developed in the course of an illness that at one time could not be distinguished from sarcoidosis. When the patients were first observed the result of a Mantoux test was negative in all but two cases. In these the test was not carried out until at least two years after the recognized onset of lesions. It is possible that in all cases the patients may be insensitive to tuberculin in the early stages of the disease.

Thus, while some cases show all the features of sarcoidosis as distinct from frank tuberculosis, great difficulty is experienced in distinguishing certain cases that present intermediate features.

Summary.

1. The history of the knowledge of sarcoidosis is reviewed in order to introduce the classical forms of the disease.

2. The histological appearance of the lesions is described and compared with that seen in other tuberculoid granulomata. The appearance is typical although not specific to this disease.

3. In 30 proved cases of sarcoidosis the symptoms, lesions, clinical-pathological findings and bacteriological investigations are described.

4. Forty-five other cases which were suspected of being sarcoidosis are used to illustrate the difficulties of diagnosis and of differential diagnosis.

5. The results of these observations are discussed. The disease is interpreted as being a chronic infective process of unknown ætiology. No positive evidence is presented to support the view that this condition is a form of tuberculosis, but some observations of significance in this respect are made.

6. Diagnostic criteria adopted at the beginning of the investigation are critically revised in the light of the experience gained. The concept is put forward that sarcoidosis is a generalized disease, having a typical histological pattern, which runs an asymptomatic course unless extensive tissue involvement is in progress or an organ of small compass is affected.

7. It is pointed out that in the present state of knowledge this condition cannot be distinguished from certain forms of tuberculosis by any criterion.

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Legends to Illustrations.

FIGURE I.—Endothelioid cell follicle in a lymph node. (× 300.)

FIGURE II.—Giant cell in an endothelioid cell follicle in a lymph node. (× 300.)

FIGURE III.—Barely palpable lymph node removed from patient in Case 54, showing scattered follicles. (× 20.)

FIGURE IV.—Section of a skin sarcoid. (× 20.)

FIGURE V.—Complete replacement of the normal tissue of a lymph node by typical follicles. (× 20.)

FIGURE XIV.—Case 7. Rarefaction of the phalanges.

FIGURE XVI.—Case 7. Subcutaneous sarcoid of Darier and Roussy seen under glass. (× 3.)

FIGURE XVII.—Case 5. Extensive diffuse infiltration of the lungs, 1944.

FIGURE XVIII.—Case 5.—Considerable clearing when compared with the state seen three years previously (Figure XVII). The diffuse infiltration is not now present, but there is an increase of the pulmonary markings of the lower zones.

FIGURE XIX.—Case 20. Biopsy of lung and pleura showing scattered sarcoid follicles and fibrosis. (× 20.)

FIGURE XX.—Case 20. X-ray film of right side of chest showing two hydatid cysts. No radiological evidence of sarcoidosis.

OCULAR MANIFESTATIONS OF SARCOIDOSIS WITH A DESCRIPTION OF SEVEN CASES.

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IN the course of an investigation which has been undertaken at the University of Melbourne into the condition of sarcoidosis (Robinson and Pound, 1950), 23 patients suffering from this disease were referred to me for examination, and of these six were found to have definite signs of ocular involvement by sarcoidosis. In one further case unilateral keratitis was present which was probably due to sarcoidosis.

Sarcoidosis may affect most tissues of the eye. It frequently is seen as uveo-parotitis, a condition first described by a Danish ophthalmologist, Heerfordt. This syndrome includes uveitis, enlargement of the salivary or lachrymal glands, cranial nerve palsies and changes in the cerebro-spinal fluid.

In the conjunctiva there may be tubercle formation. These appear as clear hyaloid or yellowish nodules, varying in size from a pin-point to a chalazion and producing no symptoms beyond an occasional mucous discharge (Osterberg, 1939). The tubercles resolve without sequelæ, although symblepharon has been described (Folk, 1940). The affection of the conjunctiva gives rise to one form of Parinaud's oculo-glandular syndrome (Parinaud, 1889). Episcleral sarcoid masses (Wilmer, 1933) and episcleritis (Lewis, 1941) may occur.

The cornea may be affected by sclerosing keratitis (Savin, 1934), *keratitis sicca* from drying of the cornea secondary to involvement of the lachrymal gland (Levitt, 1941), diffuse punctate keratitis (Folger, 1936), interstitial keratitis (Reisner, 1944), or herpes of the cornea. These lesions tend to affect the lower part of the cornea and to be accompanied by uveitis. They may resolve without scarring (Levitt, 1941) or cause a permanent opacity (King, 1939).

By far the most common lesion found is inflammation of the anterior part of the uveal tract—that is, of the iris and ciliary body—producing irido-cyclitis. This may have an insidious onset (King, 1939), with little or no pain, the patient's only complaint being blurring of vision. On examination of the eye no ciliary injection may be seen, but cells are present in the aqueous, with keratic precipitates formed by the deposition of these cells on the endothelial surface of the cornea. Usually the iridocyclitis is more severe, with pain, ciliary injection and exudate into the anterior chamber. Nodules may be present on the iris, which disappear with subsidence of the inflammation. The complications which may follow the iridocyclitis are the formation of posterior synechiæ, some atrophy of the iris, secondary glaucoma, secondary cataract (Scott and Bodley, 1938) and vitreous opacities.

Chorioiditis may be due occasionally to sarcoidosis. It then occurs most usually as small peripheral lesions (Levitt, 1941), although disseminated chorioiditis has been described.

Sarcoid infiltration may form large chorioidal tumours (Walsh, 1939)), may involve the retina (Reis and Rothfeld, 1931), or sometimes may form masses extending into the vitreous.

Perivasculitis of the retinal vessels may lead to their occlusion, with subsequent retinal hæmorrhages and even hæmorrhages into the vitreous (Goldberg and Newell, 1944).

In the optic nerve three lesions may be found—optic neuritis (Salveson, 1935), papillœdema secondary to intracranial sarcoid tumour, or direct infiltration of the nerve by sarcoid tissue (Reis and Rothfeld, 1931).

Ptosis also has been described (Garland and Thompson, 1933), as well as involvement of the orbit with sarcoid masses (King, 1939).

Reports of Cases.

In the above series of patients suffering from sarcoidosis there were seven with ocular involvement which could be attributed to this disease. Six of them had iridocyclitis; in five cases it was bilateral, in one only the eye had a nodule on the iris, in two secondary glaucoma followed the iridocyclitis. Four patients had involvement of the cornea, and in one of these a small peripheral chorioidal lesion was present in his other eye. A probable hæmorrhage into the vitreous occurred in one case with recognized iridocyclitis. In none of the cases were the lids or the conjunctivæ involved.

The case numbers are those of Robinson and Pound.

CASE 7.—C.McD., a woman, aged fifty-six years, was a proven subject of sarcoidosis for seventeen years with lesions of the skin, phalanges, lymph nodes and lungs. Her ocular symptoms commenced in 1946 with a sudden pain in her left eye due to an attack of acute glaucoma. This was found to be secondary to iridocyclitis. The visual perception was hand movements at one metre, the tension was 90 millimetres of mercury (Schiotz), and the pupil was almost completely bound down by the inflammation. A glaucoma iridectomy was performed. At operation the iris was difficult to deliver owing to the presence of posterior synechiæ.

At present the left eye has a divergent strabismus, the visual acuity in the right eye is 6/24 with correction, and in the left eye perception of hand movements only. The visual field in the right eye is full; the left field when elicited with light shows that only the temporal half of the field remains. Tension in both right and left eyes is normal—15 millimetres of mercury (Schiotz). Both corneæ are clear, and no keratic precipitates are present. The pupils are irregular (Figure I), with in the left eye (Figure II) a coloboma above due to the previous iridectomy. Both pupils dilate very poorly and irregularly after the instillation of mydriatic drops. The irides are atrophic at their pupillary margins, and no nodules are present. At the anterior surfaces of the lens capsules is some pigmented deposit, and there are thin fibrous adhesions from the posterior surface of the iris to the lens capsule. The left lens shows diffuse sclerosis. Both fundi appear normal except for the presence of glaucomatous cupping of the left disk and some vitreous opacities.

CASE 12.—R.L., a man, aged forty-six years, had a left Bell's palsy six years ago, which was followed after three days by dimness of vision of his left eye; this was due to acute iritis of the left eye, with exudate into the anterior chamber and formation of posterior synechiæ. A large nodule could be seen on the iris at the six o'clock position. Dense vitreous opacities were also present. Seven weeks after the onset a right facial paralysis developed, but both facial paralyses cleared after three weeks. Five months from the onset the patient developed a left cornal ulcer which he attributed to a hit in the eye with a piece of nail. The ulcer failed to heal until a lateral tarsorraphy was performed. Enlarged superficial glands were present, biopsy of which confirmed the diagnosis of sarcoidosis. X-ray examination of the chest showed widespread mottling throughout the lungs.

Present ocular examination reveals that the visual acuity of the right eye is 6/5, while that of the left is limited to the counting of fingers at three feet. In the right fundus *is a small peripheral patch of old chorioiditis.* The eye is otherwise normal and the peripheral field of vision full.

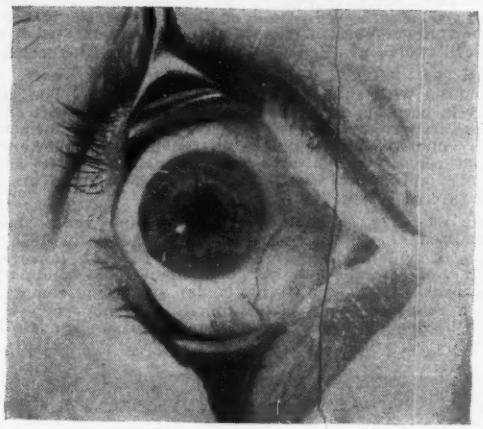

FIGURE I.[1]

Case 7. Right eye showing poorly dilated, irregular pupil and fibrous posterior synechiæ.

The left eyelids are still apposed with the lateral tarsorraphy (Figure III). The cornea is opaque over its lower third, with diffuse speckled whitish dots, the size of pinheads, placed in circumscribed areas *forming well-defined plaques* in the superficial portion of the cornea. There is superficial and deep vascularization of this region of the cornea, and it does not stain with fluorescein. The upper level of the opacity is well demarcated, and the sensation of the upper two-thirds of the cornea is normal. The iris is atrophic, no

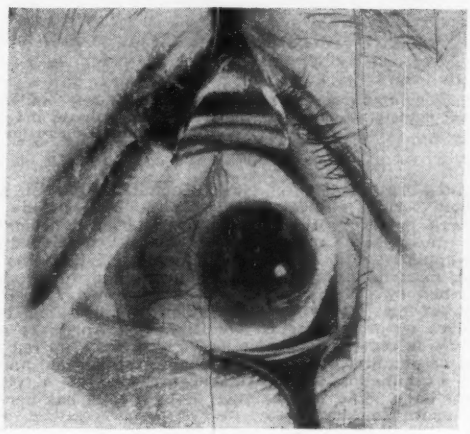

FIGURE II.

Case 7. Left eye with iridectomy and presence of posterior synechiæ and lens sclerosis.

nodules are present, but posterior synechiæ have formed and the lens is developing a secondary cataract. The parotid glands have not been enlarged at any time.

CASE 18.—S.B., a man, aged thirty-four years, developed enlargement of the superficial lymph nodes of the body and a diffuse infiltration of the lungs nine years ago. A gland biopsy at this time showed the changes of sarcoidosis, as did a section from an enucleated tonsil.

[1] All photographs were taken after mydriatics had been instilled.

Five years ago his ocular symptoms commenced with recurrent attacks of acute iritis of his right eye, which were accompanied by severe pain. The first attack was apparently precipitated by the removal of a corneal foreign body. The left eye also became affected two years ago.

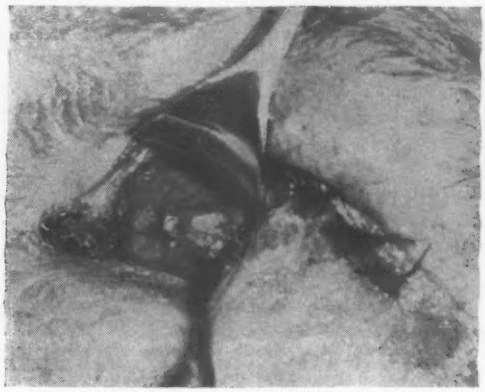

FIGURE III.

Case 12. Left eye. The lids are joined laterally. The lower third of the cornea has speckled opacities and some vascularization.

At present the visual acuity of the right eye is 6/6 partly, and of the left 6/9 with correction. In the right eye (Figure IV) the cornea is hazy over *its lower one-tenth.* The opacity is associated with deep vascularization, and old pigmented keratic precipitation can be seen. The pupil is irregular and reacts poorly owing to the presence of fibrous posterior synechiæ. The iris is atrophic at the pupillary margin, and pigmentary deposits are present on the anterior surface of the lens capsule. The fundus is normal, with some vitreous opacities, but there is no evidence of any active inflammatory process.

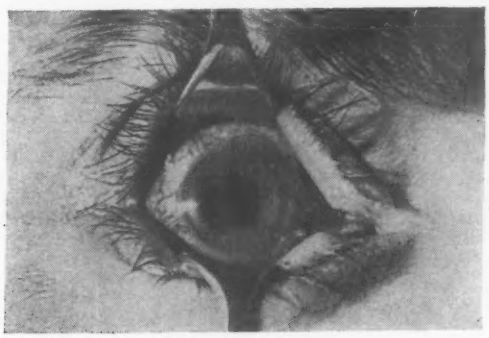

FIGURE IV.

Case 18. Right eye, showing corneal opacity over lower tenth. Irregular pupil with fibrous posterior adhesions.

The left eye (Figure V) is symptomless with no injection of the conjunctiva. The pupil reacts normally and actively and dilates fully after instillation of homatropine drops. The fundus is normal, but the outlines are indefinite owing to the presence of fine vitreous opacities. With slit-lamp examination fine keratic precipitates, an aqueous flare with cells in the anterior chamber and vitreous, can be seen. There is no dilatation of the vessels of the iris, and its pattern is clear.

CASE 24.—M.P., a woman, aged forty-eight years, developed bilateral iridocyclitis three years ago with secondary glaucoma, which commenced with pain and injection of the left eye. In the right eye the symptoms were those of seeing coloured circles around lights; there was no pain.

Her vision became blurred, and despite treatment with atropine, subconjunctival mydricaine and intramuscular milk injections, the tension remained elevated—in the right eye 70 and in the left eye 40 millimetres of mercury (Schiötz). Operations to relieve the glaucoma followed. A right

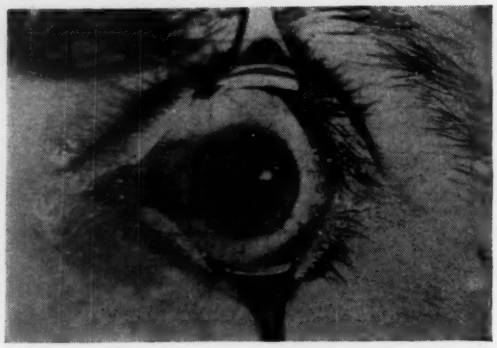

FIGURE V.

Case 18. Left eye. Appearance of the eye is normal. The pupil is fully and regularly dilated.

trephine operation reduced the intraocular tension to normal. The tension of the left eye, however, was not permanently reduced until a left trephine operation, La Grange sclerectomy and a further corneo-scleral trephine operation had been performed at intervals.

At present the intraocular tension is normal, being 22 millimetres of mercury (Schiötz) in both eyes, and her visual acuity, which was previously defective (6/60 in both eyes), has now improved to 6/18 in the right eye and 6/9 in the left eye. The left field of vision is full to 1/330 white; the right has some concentric constriction with an increase of lower nasal loss. In the right eye (Figure VI) the cornea is clear; there are some fine old keratic precipitates deposited

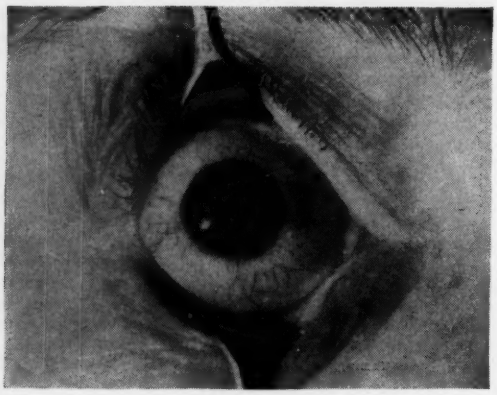

FIGURE VI.

Case 24. Right eye showing irregular, poorly dilated pupil with partial iridectomy above.

on its endothelial surface. The pupil is small and dilates irregularly with mydriatics, owing to posterior synechiæ. The iris itself is somewhat atrophic and has a small defect above, due to the peripheral iridectomy of the previous operation. Slight opacities in the lens and vitreous can be seen, and the fundus is normal.

The left eye (Figure VII) shows the drainage channels of the previous operations. Posterior synechiæ involve portion of the pupillary border of the slightly atrophic iris and occur along the pillars of the old iridectomies. The vitreous, which previously was hazy from vitreous opacities, has now cleared. The polychromatic lustre typical of a complicated cataract can be seen. The fundus is normal.

Routine X-ray examination of the patient's chest in 1946 showed large glandular masses in both hilar regions. There has been no other evidence of sarcoidosis, so that it has been impossible to prove that she is definitely suffering from the disease. However, clinically the diagnosis seems justified.

The great improvement in her ocular findings has been associated with a regression of the size of the glandular swelling of the chest. The patient has been treated during the past twelve months with 30,000 units of calciferol daily.

CASE 59.—E.B., a man, aged thirty-six years, has sarcoidosis with skin, gland and chest lesions. The visual acuity in both his eyes was found to be 6/5. The left cornea had a triangular area of superficial opacity measuring one by one by one millimetre on the nasal and lower side of the cornea, which was not vascularized. It had a brownish appearance due to slight pigmentation. This may be a sarcoid lesion.

CASE 66.—E.G., a man, aged thirty-nine years, had a generalized enlargement of the lymph nodes in 1935, the nature of which was not recognized. In 1944, however, a lymph node section showed the histological findings of sarcoidosis. Early in 1948 his ocular symptoms commenced with a relatively painless inflammation of his left eye, for which he did not seek attention for several weeks. He then

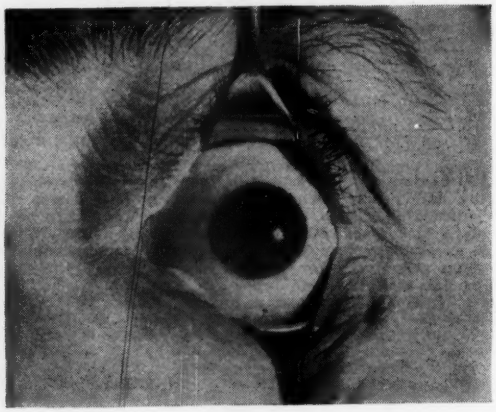

FIGURE VII.

Case 24. Left eye. The pupil again is poorly dilated. A complete coloboma of the iris present above and a partial coloboma below from the previous operations to relieve the secondary rise in tension.

consulted Dr. Pittar, of New Zealand, to whom I am indebted for his clinical notes. Plastic iritis of his right eye was present with pronounced posterior synechiæ and some fine keratic precipitates. The eye quietened with local application of atropine. In November, 1948, the iritis flared up again, and in December the right eye also showed inflammatory changes of the iris. In January, 1949, the vision of his left eye became much worse owing to the presence of gross vitreous opacities. In April the visual acuity was reduced to perception of light only, no red reflex could be obtained on ophthalmoscopic examination, and slit-lamp examination suggested the presence of a vitreous hæmorrhage. The inflammation of both eyes has persisted, varying in intensity.

At present the visual acuity in his right eye is 6/6, and in his left 6/12 partly. The visual fields are full. The right pupil is dilated regularly and fully with atropine. With slit-lamp examination many cells are seen circulating in the aqueous, and large "mutton-fat" keratic precipitates are deposited on the endothelial surface of the cornea along its lower periphery. Small rounded whitish-yellow nodular patches are present around the pupillary border of the iris, appearing from its posterior surface and extending beyond its margin to be attached to the lens, forming posterior synechiæ. There are no tubercles in the iris substance. The fundus is normal.

The left pupil is irregular, the atrophic iris being bound down by posterior synechiæ. Many cells are present in the anterior chamber, and large "mutton-fat" keratic precipitates have formed. The inferior one-sixth of the anterior chamber is filled by a mass of plastic exudate. No details of the

fundus could be obtained through the poorly dilated pupil and the dark vitreous haze.

CASE 75.—C.H., a man, aged twenty-seven years, was examined by me three months after the onset of his illness, which commenced with an attack of acute iridocyclitis of his right eye. Two weeks later a right facial paralysis of the lower motor neuron type supervened and was followed nine days later by a complete paralysis of the left side of his face. On routine eye examination iridocyclitis had been noted in his left eye the previous day. The exposure of his right cornea necessitated a right tarsorraphy. Recently his hearing has become poor. The presence of sarcoidosis was proven by liver biopsy.

At present he has a complete right facial paralysis with a lateral tarsorraphy. The left facial paralysis is incomplete: the patient is able to retract the angle of his mouth, and on his attempting to shut his eyes the cornea is covered by his upper lid. The visual acuity of the right eye is 6/18, and of the left eye 6/24 without correction. The right cornea is clear, but in the left there is at the lower border a small patch of deep keratitis with new vessels passing into the posterior third of the cornea. Right bilateral plastic iridocyclitis is present with numerous keratic precipitates of "mutton-fat" type deposited on the corneal endothelium. The aqueous and vitreous both contain numerous cells. The pupils are enlarged fully and regularly by atropine, but many dilated iris vessels are visible in the muddy irides. No nodules are present in the iris tissue. There are early posterior synechiæ and some iris pigment on the anterior surfaces of both lenses. The fundi are normal.

There has been no pain or swelling of the salivary or lachrymal glands at any time.

Conclusions.

The series of cases is as yet too small to permit of definite conclusions being drawn; nevertheless, the following points should be noted.

In the patients examined with uveitis and facial paralysis there was no enlargement of the parotid glands at any time; this is unlike the description of the typical Heerfordt's syndrome. In long-standing cases in the series the iris appeared atrophic on the inner third.

The visual end results in many cases in which the condition became quiescent are good, and the eyes affected with sarcoidosis appear to react well to operation.

The eyes in our series have not progressed to destruction, as often occurs with tuberculous inflammation.

In cases of iridocyclitis sarcoidosis should be considered as a cause and especially suspected in the presence of the "mutton-fat" type of keratic precipitate, nodules in the iris or Koeppe's nodules on the pupillary margin. Sarcoidosis is a generalized disease, and examination should be made for manifestations elsewhere, as enlargement of the lymph nodes and involvement of the lung, skin or bones. A negative response to the Mantoux test is of aid in the forming of a diagnosis, although a positive response does not exclude sarcoidosis.

The treatment in these cases is the routine treatment for iridocyclitis, but the effects of calciferol in some cases should not be forgotten.

Summary.

1. A review has been made of the ocular lesions found in sarcoidosis.

2. The ocular changes in seven cases are given.

Acknowledgements.

I am indebted to Dr. Bruce Robinson for giving me the opportunity of examining these patients, to those many oculists who assisted with clinical notes, and to Mr. R. Inglis, clinical photographer at the Royal Melbourne Hospital, for his excellent photographs.

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Reports of Cases.

MULTIPLE MYELOMA: TWO CASES WITHOUT BONY CHANGE ON RADIOLOGICAL EXAMINATION.

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Sydney Hospital, Sydney.

MULTIPLE MYELOMA has been defined as a malignant tumour arising in the bone marrow, which tends to occur in persons after the fifth decade (Sturgis, in Cecil's "Text Book of Medicine"). This definition is in agreement with the modern concept of this disease as a proliferation of plasma cells in the marrow, with a predilection for those areas most active in blood-cell formation. That such proliferation is not always associated with lytic destruction of bone and changes in the appearance of the skeleton on radiological examination has been recognized in the literature.

In the two cases of myelomatosis described, no changes in the bones were found on X-ray examination.

Case I.

N.P., aged fifty-three years, an ex-sailor, was admitted to hospital with the diagnosis of "anæmia—for investigation". Three months prior to his admission he had been in his usual health, and in the course of his occupation as wharf labourer had been able to lift sacks weighing 150 pounds without distress. He was treated then for a respiratory ailment, and productive cough during this episode lasted about three weeks. He did not "pick up", and increasing weakness and tiredness became apparent; these symptoms, with progressive exertional dyspnœa and palpitations, prevented resumption of work. Increasing pallor of mucous membranes, and darkening and drying of skin exposed to the sun, were noted during the three months before his admission to hospital. Progressive anorexia was associated with the loss of one stone in weight. He had neither bone pains nor neurological symptoms. Past illnesses included a "bubo" of the right

groin, incised in France in 1915. No primary sore was present, and the patient stated that a Wassermann test performed three months later had produced a negative result. Malaria, contracted in 1917, was alleged to have recurred intermittently until 1942. There was no history of previous renal disease. The patient had been a heavy smoker of tobacco and drinker of alcohol.

Physical examination revealed considerable pallor of the mucous membranes and a peculiar muddy to bronze colour of the exposed areas of skin. No pigmentation of the buccal mucosa or of the skin of the axillæ was observed. A generalized impetiginous rash, which was itchy, had been present for three weeks; this was relieved after treatment with penicillin administered parenterally and oral sulphonamide therapy. Loss of weight was not obvious, and the patient did not appear seriously ill. His pulse rate was 100 per minute and regular; the radial vessel wall was palpable. The blood pressure was 140 millimetres of mercury, systolic, and 90 millimetres of mercury, diastolic. The heart was not enlarged on clinical examination; a blowing systolic murmur was present in the aortic area. A firm, smooth liver edge was palpable one and a half inches below the costal margin; the tip of the spleen was also palpable. There were a few discrete lymph glands in the groins and axillæ, which may have been due to the skin infection. Rectal examination revealed no abnormalities. The urine contained albumin in varying amounts, and the specific gravity was also variable (1010 to 1020). The figures for hæmoglobin value and non-protein nitrogen content of the blood are shown in the graph (Figure I). A typical blood count shortly after the patient's admission to hospital gave the following results. The hæmoglobin value was 5·8 grammes per 100 millilitres of blood. The hæmoglobin content of individual cells was normal. Moderate anisocytosis was present; a few small and large cells and an occasional stippled cell were seen. Platelets were not numerous. The leucocytes numbered 5700 per cubic centimetre; 62% were neutrophile cells, 26% lymphocytes, 1% eosinophile cells, 2% basophile cells, 5% monocytes, 2% neutrophile-myelocytes and 2% metamyelocytes. Numerous band forms and an occasional Turck cell were present. The blood sedimentation rate was 120 millimetres in one hour (Westergren).

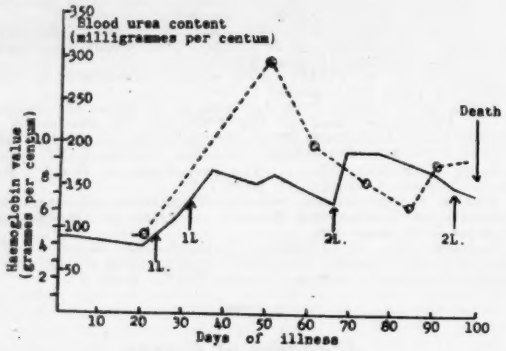

FIGURE I.
Results of hæmoglobin and blood non-protein nitrogen estimations in Case I.

The results of further laboratory investigations were as follows. The Wassermann reaction and the Kahn flocculation reaction were completely positive. This result was unaltered after two courses of penicillin, totalling 6,000,000 units. Occult blood was found in the fæces on two occasions; no cysts or ova were detected. Bence-Jones proteose was at no stage detected in the urine, and complete X-ray examination of the skeleton revealed no abnormality (Dr. H. G. Marsh). X-ray examination of the chest showed the lung fields to be clear. The cardiac shadow was within normal limits; a small plaque of atheroma was present in the aortic arch, and some widening was observed (Dr. J. E. Aiken). On the patient's admission to hospital, the total serum protein content was 6·9 grammes *per centum*—5·5 grammes of albumin and 1·4 grammes of globulin. One month later the total serum protein content was 6·5 grammes *per centum*. The findings in one of the myelograms were as follows. A differential count (500 cells counted) gave the following results: 0·2% neutrophile myelocytes, 0·4% metamyelocytes, 2·0% neutrophile polymorphonuclear cells, 3·4% reticulum cells, 0·4% polychromatic normoblasts, 15·8% mature lymphocytes, 46·0% atypical lymphocytic cells, 31·4% naked nuclei, and 0·4% atypical binucleated cells.

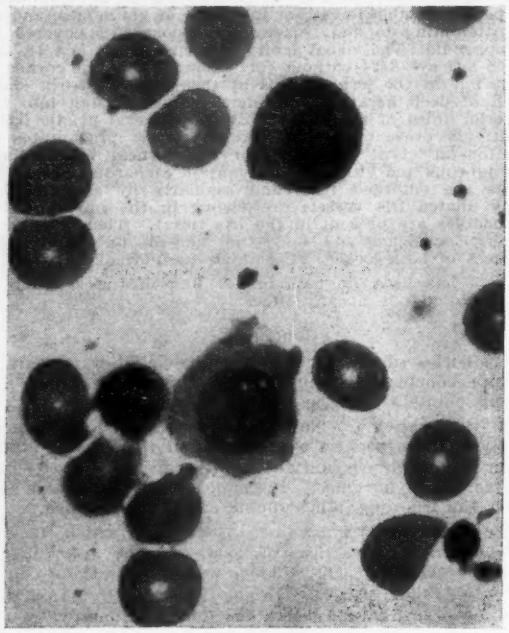

FIGURE II.
Marrow film.

The report on the sternal marrow puncture (Dr. G. A. W. Johnston) was as follows:

> The cellularity of the marrow is markedly increased. Granulopoiesis and erythropoiesis are greatly diminished. Of those cells which could not be identified with certainty, some resembled cells of the lymphocyte series and others myeloma cells at different stages of maturation.

(Figure II is a typical field of the bone marrow smear.) Dr. Johnston was unable to establish the diagnosis on sternal marrow smears alone, and recommended sternal marrow biopsy, which was refused by the patient. Microscopic examination of urinary deposit, on eight occasions, revealed only a few pus and red blood cells. Excretion pyelography showed little visible renal function after one hour (Dr. D. G. Maitland).

Persistent vomiting developed one month after the patient's admission to hospital, and from then onwards his condition steadily deteriorated, in spite of parenteral liver therapy, and treatment with iron, polyvitamin preparations and blood transfusions (see Figure I). He died, two months after entering hospital, after a cerebral vascular catastrophe. Despite increasing weakness he was ambulant until two days before death, and was apyrexial throughout.

Biopsy of a lymph gland in the left groin was performed. Dr. A. A. Palmer's report on the section was as follows: "There is thickening of the capsule with sinus catarrh and plasma cells are abundant in the medulla. The appear-

ances suggest active subacute inflammation." (In view of the subsequent diagnosis of myelomatosis, this section was reexamined. The possibility was considered that the plasma cells might be the result of infiltration of the medulla. However, the presence of sinus catarrh and of occasional eosinophile cells supports the original comment. Furthermore, the positive Wassermann reaction may have played some part in producing this picture.)

In his autopsy report, Dr. B. W. Donnan reported the presence of (i) syphilitic aortitis, (ii) nephrosclerosis of undetermined origin, (iii) pulmonary emphysema and fibrosis, and (iv) a small left frontal subarachnoid hæmorrhage. Significant microscopic findings were as follows. (i) In the bone, the marrow had been largely replaced by cells resembling plasma cells, some lying outside the periosteum. The appearances were typical of multiple myeloma (see Figure III). (ii) In the kidney, diffuse cortical fibrosis is present with atrophy of the tubules. Some of these tubules contained homogenous pink-staining material. The changes were similar to those described in multiple myeloma with renal involvement (see Figure IV).

Case II.

L.K., aged fifty-five years, had been engaged in heavy labouring work until nine months prior to examination. He had been well until four years prior to examination (1945), when he noticed attacks of colicky, mid-line abdominal pain; each attack lasted nine to twelve hours and was associated with some vomiting and with the passage of several brown fluid motions. Attacks were more frequent after a hæmatemesis two years prior to examination; radiological investigation of the alimentary tract at that time revealed no abnormality. In December, 1945, a fixed, hard mass of glands appeared in the left groin. Biopsy of one of these glands was performed and the report (Brisbane General Hospital) was as follows:

> There has been some inflammation followed by organization and fibrosis. Much adipose tissue was involved. The small amount of lymphoid tissue found was being invaded by the fibrosing process.

There had been no subsequent lymphadenopathy. Weight lost since 1945 totalled four stone; the loss of weight had been more rapid during the past nine months owing to extreme anorexia. Exertional dyspnœa, with increasing fatigue, had been present for some months, and more recently, slight peripheral œdema had been noticed. Laparotomy early in 1945 revealed much clear, straw-coloured fluid in the abdominal cavity. One loop of small bowel, approximately eighteen inches long, was hypertrophic and œdematous. No operative procedure was undertaken and the abdomen was closed. Appendicectomy was performed later in the same year. The blood failed to react to the Wassermann test (Brisbane General Hospital report).

Examination showed the patient to be a pale, anxious-looking man with signs of recent loss of weight. The pulse rate was 88 per minute and irregular. The systolic blood pressure was 110 millimetres of mercury, the diastolic pressure 55 millimetres. The spleen was palpable three fingerbreadths below the left costal margin; a smooth liver edge was barely palpable, and there was no significant enlargement of the superficial lymph glands. No further abnormality was detected in the alimentary or any other system. The patient was afebrile while in hospital.

Laboratory investigations gave the following information. X-ray examination of the chest showed the lungs to be clear. There was some spondylitis of the thoracic part of the spine. Radiological examination of the skeleton showed no evidence of myelomatosis or secondary neoplasm (Dr. H. G. Marsh). The total serum protein content was 10·2 grammes per 100 millilitres—3·9 grammes of albumin and 6·3 grammes of globulin. The result of the Wassermann test was anti-complementary on two occasions (possibly owing to the presence of hyperglobulinæmia); the Kahn flocculation test result was negative. Renal function test results were within normal limits. The blood urea content was 12 milligrammes per 100 millilitres, the blood creatinine content was one milligramme per 100 millilitres, while the result of the urea concentration test was 85% of normal standard. The fat content of the fæces was 43% (dried weight), 32% being split fat and 11% unsplit fat. Microscopic examination of a centrifuged urinary deposit revealed an occasional hyaline cast and pus cell, also 10 to 15 red blood cells per high-power field. Liver function tests indicated early parenchymatous damage. Thymol turbidity was 20 units, hippuric acid excretion 4·5 grammes in four hours. The alkaline phosphatase level in the serum was increased to 0·09 Kay unit and the Van den Bergh reaction was within normal limits. On the patient's admission to hospital the hæmoglobin value was 7·7 grammes per 100 millilitres of blood. The hæmoglobin content of individual cells was normal, and moderate anisocytosis and pronounced macrocytosis were present. The leucocytes numbered 4900 per cubic millimetre, and had a normal distribution curve. The blood sedimentation rate was 138 millimetres in one hour (Westergren). Sternal puncture was performed, the findings in the myelogram being as follows. Of 500 cells counted, 0·4% were myeloblasts, 2·4% premyelocytes, 13·4% myelocytes, 14·0% metamyelocytes, 18·8% polymorphonuclear cells, 4·4% lymphocytes, 2·6% monocytes, 30·2% plasma cells, 0·4% reticulum cells, 12·6% normoblasts, and 0·8% mitotic figures. The comment was as follows:

> The cellularity of the marrow is within normal limits. Granulopoiesis and erythropoiesis are proceeding along normal lines. The outstanding feature is the great increase in plasma cells, which is diagnostic of multiple myeloma.

While in hospital this patient received one and a half litres of blood, with the result that the hæmoglobin value increased to 10·2 grammes *per centum*. Symptomatic treatment was prescribed, and he was discharged in a fair state of health.

Comment.

As Evans has noted in a recent article on multiple myeloma, the increasing number of cases reported probably reflects improved diagnostic methods rather than increased prevalence of this condition; sternal marrow puncture and biopsy are the most important of these aids. In the case of N.P., however, although the diagnosis was suspected and post-mortem examination of sections of bone marrow revealed extensive myelomatous infiltration, three successful sternal marrow punctures during life failed to reveal recognizable myeloma cells. When the condition is strongly suspected and the sternal marrow smear does not confirm the diagnosis, it is justifiable to perform an iliac or rib puncture (Johnston).

Some authors, while recognizing that anæmia is a common feature of the disorder, consider that it seldom becomes severe. Lichtenstein and Jaffe, however, note that several of their patients showed severe anæmia when first investigated, and state that repeated blood transfusions have only a temporary sparing effect. Both patients under discussion had anæmia and loss of weight; N.P. also emphasized the transient benefit obtained from blood transfusion when the marrow is extensively infiltrated with myeloma cells.

Hyperglobulinæmia is a feature in 50% of cases, according to Lichtenstein and Jaffe. These authors postulate that increased blood sedimentation rate and rouleaux formation of erythrocytes are largely due to this factor. Bayrd and Hoek found a tendency towards rouleaux formation in 38 of 63 cases, and commented on the absence of this finding when the globulin content of the serum was normal. Whitby and Britton, on the other hand, attribute rouleaux formation and associated phenomena to an increase in the fibrinogen content of the plasma. N.P., whose serum contained a normal amount of protein, with a normal albumin-globulin ratio, showed a tendency toward rouleaux formation and a greatly increased erythrocyte sedimentation rate. The plasma fibrinogen content may have been of interest in this case.

In neither case was Bence-Jones proteose found in specimens of urine tested. It must be admitted, however, that urine collected over a twenty-four-hour period was not examined for this constituent, as recommended by Lichtenstein and Jaffe.

Consideration was given to the possibility that N.P. may have been suffering from anæmia secondary to chronic renal disease. However, this diagnosis was thought to be untenable in the absence of hypertension and cardiac hypertrophy. It is of interest that Foord *et alii* have described renal involvement preceding skeletal changes in multiple myeloma with relatively early azotæmia.

Conclusion.

In conclusion, it may be stated that radiological examination of the skeleton will neither confirm nor exclude the diagnosis of myelomatosis. Just as a final diagnosis of pulmonary tuberculosis is not made until the tubercle bacillus has been identified, so also a final diagnosis of multiple myeloma should not be made until plasma cells or their precursors have been found in significant numbers in a marrow smear or biopsy.

Acknowledgements.

These patients were under the care of Dr. W. Evans and Dr. A. McGuinness. My thanks are due to them, and to the Medical Superintendent of Sydney Hospital, for permission to publish this report, and also to the staff of the Kanematsu Institute of Pathology for the photomicrographs.

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THE "LATERAL ABERRANT THYREOID": REPORT OF A CASE.

By Gordon Kerridge,

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The nature of laterally situated tumours of thyreoid tissue in the neck has, for some years, excited the interest of many workers. Out of the controversy have arisen two major hypotheses. The first is that such tumours have a developmental origin from the lateral thyreoid *Anlagen*, this being the view supported by Lahey (1946), and until recently by Crile (1939). Those opposing this hypothesis believe that the so-called lateral aberrant thyreoid is a metastasis in a cervical lumph gland from a small unsuspected carcinoma of the corresponding lobe of the thyreoid. The protagonists of this theory include such writers as Dunhill, Willis, King and Pemberton, Warren and Feldman, and of recent years, Crile (1947).

The following case is presented as one further link in the chain of evidence supporting this latter hypothesis.

Clinical Record.

Mr. A.U., aged forty years, a mental defective, was admitted to the Royal Hobart Hospital on July 26, 1949, complaining of a lump on the left side of the neck, present for some years. The exact period was impossible to ascertain, but was believed to exceed five years. The lump was painless, and had been growing slowly. There were no other symptoms.

On examination, the patient was well nourished and his physical health appeared good. A large mass was present in the posterior triangle on the left side, measuring 10 centimetres vertically and seven centimetres horizontally. This swelling was smooth and firm on palpation. The skin was freely movable, but the tumour appeared to have some attachments deep to the posterior border of the sterno-mastoid muscle. A number of investigations were undertaken. A blood count showed that the hæmoglobin value was 14·4 grammes per 100 millilitres and that the leucocytes numbered 8000 per cubic millimetre, the differential leucocyte count giving normal results. There was no reaction to the Wassermann or Kline test. Radiographs of the chest revealed no abnormality. Radiographs of the neck were not satisfactory, as the patient became refractory.

The first operation was performed on July 29, 1949, under endotracheal cyclopropane and oxygen anæsthesia. A horizontal supraclavicular approach to the tumour was adopted, the sterno-mastoid muscle being divided. The tumour was seen to contain cystic areas, and closely resembled thyreoid tissue. It was adjacent to the internal jugular vein, but was removed with little difficulty. No other lymph glands were enlarged. The thyreoid gland was palpated, the left lobe being visualized, and was clinically normal and small. The wound was closed in layers, drainage being instituted for twenty-four hours after operation.

The tumour, measuring 10 centimetres by 7 centimetres by 5 centimetres, possessed a fibrous capsule. The cut surface was spongy in texture and contained many minute yellow nodules, giving rather the appearance of fish roe. Microscopic examination of sections revealed the growth to be a papillary tumour in which thin cords were lined by a single layer of cubical epithelium. In some areas there was alveolar formation, a few of these alveoli containing a poorly staining eosinophilic substance which in some ways resembled thyreoid colloid. The yellow nodules seen macroscopically were areas of necrosis. The general appearance did not suggest malignant change, but the tumour's resemblance to a cystadenoma of the thyreoid was noted (see Figure I).

Convalescence was uneventful, and after confirmation by the pathologist of the diagnosis of "lateral aberrant thyreoid", it was decided to perform hemithyreoidectomy. This decision was made despite the fact that the homolateral lobe had been examined at operation—the final deciding factor being the following dogmatic statement by Willis: "A lateral aberrant thyroid calls for hemithyroidectomy, and, if this is done, a small carcinoma will always be found, if searched for, in the excised lobe."

A second operation was undertaken on August 23, 1949, under endotracheal cyclopropane and oxygen anæsthesia, and the thyreoid was again explored. A collar incision was made, the "strap muscles" being divided on the left side. The gland was smaller than usual, and no abnormality was apparent. The left lobe and isthmus were removed completely, the recurrent laryngeal nerve being visualized and preserved. The wound was closed in layers with drainage.

The uncut surface of the specimen appeared normal and the lobe was of normal size. Examination of sections revealed a whitish rounded area in the postero-inferior portion of the lobe, one centimetre in diameter, which was firm in texture and homogeneous in nature. Microscopic examination of this area revealed a papillary tumour bounded by a pseudo-capsule of compressed thyreoid tissue, the section closely resembling the tumour previously removed from the posterior triangle (see Figure II).

Subsequent progress was uneventful, the patient being discharged from hospital on August 30, 1949.

Discussion.

Papillary adenocarcinoma of the thyreoid is notoriously slow growing and of low-grade malignancy, characteristics which are equally features of the metastases in the glands of the neck. Frequently patients have reported with "lateral aberrant thyreoid" tumours of five to ten years' duration, and so the mere fact that a patient is alive

and well five years after removal of such a tumour is not conclusive evidence against the existence of a small primary growth in the thyreoid. Crile's series of 21 cases (1947) in all of which carcinoma was present in the homolateral lobe—a series sufficiently convincing to change the view of one of the most ardent protagonists of the "developmental" hypothesis—must surely be significant.

The prognosis after removal of the secondary deposits and hemithyreoidectomy is good, many patients living as long as twenty years, so that more radical operations with a higher operative mortality rate would not appear justified. Post-operative irradiation is advised by many, as these tumours are usually moderately radio-sensitive.

Summary.

1. A case of the so-called "lateral aberrant thyreoid" tumour is presented, this proving to be a secondary deposit from a small unsuspected papillary carcinoma of the thyreoid gland.

2. The importance of performing routine hemithyreoidectomy in cases of this type is stressed, even if the lobe appears macroscopically normal, as in this case.

3. The findings of Willis and of many others have been verified in this further case.

Acknowledgements.

I must thank Dr. A. Ormond Green for permission to treat this patient, who was admitted to hospital under his care. I am indebted to Dr. W. R. Pitney and Dr. Campbell Duncan for their pathological reports and for the interest which they showed in this case.

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Reviews.

A TEXT-BOOK OF OBSTETRICS AND GYNÆCOLOGY.

A "COMBINED TEXTBOOK OF OBSTETRICS AND GYNÆCOLOGY", first published in 1923, has now reached its fifth edition and its popularity is well deserved.[1] This well-known British book, which is intended for the use both of students presenting themselves for qualifying examinations and of the general practitioner, has been brought thoroughly up to date. Professor Dugald Baird is the present editor and fourteen professors and teachers of wide experience are contributors.

Baird stresses the advantage of a combined text-book of obstetrics and gynæcology, and points out that a sound knowledge of obstetrics forms an essential part of the training of a gynæcologist on account of the numerous points at which the two subjects overlap. A special section is devoted to this question.

Several new sections dealing with stillbirths, infant mortality, and psychological factors in obstetrics and gynæcology have been introduced into this present edition. The psychological section is very well set out and it should encourage the reader to realize the importance of estimating the character, the temperament and the life of each individual patient. A great deal of space is given to the practical details of treatment, general management and investigation, which will prove most helpful to the student and general practitioner. It is gratifying to see the importance of preventive treatment brought into such prominence.

The authors follow the conservative teaching of the British school in regard to endocrine therapy, and the dangers of indiscriminate and haphazard use of the hormones are stated. The obstetrical and gynæcological operative sections do not include full technical details, but yet give a sufficient guide to the general principles of the operations.

This book is attractively set out and well illustrated and can be recommended to both medical students and medical practitioners. The only adverse criticism is in regard to the size of the volume—over fourteen hundred pages make a large bulky book, difficult to carry about and also difficult to read with any degree of comfort. These disadvantages could be readily overcome if the book was divided into two volumes, and this would not interfere with the combined aspect of the work if the publishers made it obligatory to purchase the two volumes together.

[1] "Combined Textbook of Obstetrics and Gynæcology for Students and Practitioners", edited by Dugald Baird, B.Sc., M.D., D.P.H., F.R.C.O.G.; Fifth Edition; 1950. Edinburgh: E. and S. Livingstone, Limited. 9¼" × 6¼", pp. 1428, with 594 illustrations. Price: 70s.

A YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY.

A USEFUL feature of "The 1949 Year Book of Dermatology and Syphilology"[1] is the introductory article on *acne vulgaris*, contributed by the editors, Marion B. Sulzberger and Rudolf L. Baer; it is comprehensive, essentially practical and likely to be helpful to any medical practitioner faced with the management of this troublesome condition. The collected abstracts are grouped, as in the previous volume of the series, into chapters on treatment and prevention (exclusive of venereal diseases), X-ray and other physical therapy, eczematous dermatitis and urticaria (allergic and non-allergic) with general allergic conditions, drug eruptions (allergic and non-allergic), miscellaneous hæmatogenous dermatoses, other dermatoses, cancers, precanceroses and other tumours, *mycosis fungoides* and leuchæmia, fungous infections, other infections and infestations, venereal diseases (exclusive of gonorrhœa), investigative studies and miscellaneous subjects. The abstracts, which are taken from journals received by the editors between November, 1948, and December, 1949, cover a wide range of material. The number of European journals covered is notable. Outstanding advances in therapy are seen or foreshadowed in reports on ACTH, cortisone and other like steroids, which offer considerable promise in certain intractable skin diseases, and on the extended use of the antibiotics, alone or with other substances, and notably in the penicillin therapy of syphilis. The chapter on investigative studies, which is much the longest in the volume, contains a good deal that is interesting and important; many thoughtful readers will find this the most acceptable part of the Year Book. However, there is little chaff in any of the chapters, and any practitioner who has to deal with skin affections and venereal diseases (other than gonorrhœa) will find good grain for the winnowing.

A YEAR BOOK OF ENDOCRINOLOGY, METABOLISM AND NUTRITION.

THE outstanding advance of the past year or so in the field of endocrinology, the development of cortisone and ACTH, is prominent in "The 1949 Year Book of Endocrinology, Metabolism and Nutrition".[2] As in previous years, this volume opens with a chapter on the pituitary gland as the first item in the section on endocrinology; and to this chapter the editor of the section, Willard O. Thompson, contributes a brief but informative introduction dealing with ACTH (and incidentally with cortisone), following it with abstracts of some 17 papers on the subject. Then the other main known hormones of the anterior pituitary lobe are

[1] "The 1949 Year Book of Dermatology and Syphilology (November, 1948-December, 1949)", edited by Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D.; 1950. Chicago: The Year Book Publishers. 7" × 5", pp. 514, with 76 illustrations. Price: $5.00.

[2] "The 1949 Year Book of Endocrinology, Metabolism and Nutrition (December, 1948-January, 1950)"; Endocrinology edited by Willard O. Thompson, M.D.; Metabolism and Nutrition edited by Tom D. Spies, M.D.; 1950. Chicago: Year Book Publishers, Inc. 7" × 4¾", pp. 550, with illustrations. Price: $4.75, post paid.

considered in turn, with concluding material on the posterior lobe. A chapter on the thyreoid gland follows, the most notable of the abstracts being those on the role of radioactive iodine in the diagnosis and treatment of diseases of the gland. The chapter on the parathyreoids is brief this year, but the adrenals have a large place; recent work in the investigation of the cortex is included, with special reference to cortisone, and a number of abstracts deal with Addison's disease, especially in relation to *diabetes mellitus* and pregnancy. Three more chapters complete the section; one on the testes includes a paper by K. B. Fraser, of Brisbane; a relatively long chapter on the ovaries covers important advances in the understanding of ovarian function; a short "miscellaneous" chapter consists in fact of three abstracts dealing with the thymus.

The editor of the section on metabolism and nutrition, Tom D. Spies, has grouped his material, as usual, into chapters on the pancreas and liver, the alimentary tract, the hæmatopoietic, cardio-vascular, genito-urinary, dermal and skeletal systems, malnutrition and undernutrition, and therapy. Australian authors represented are Ian Wood *et alii*, of Melbourne, and J. W. Lee and E. J. Underwood, of Adelaide. This section, like that on endocrinology, contains much important and informative material. The sphere of interest of the Year Book in general is that of the medical profession at large rather than any particular specialist or group of specialists.

THE SURGICAL TREATMENT OF FACIAL INJURIES.

A WELL-PRODUCED and profusely illustrated volume of some five hundred pages by Kazanjian and Converse has been published by the Williams and Wilkins Company.[1]

The subject matter of the book is indeed wide, far wider than the title would suggest or perhaps warrant. Like so many other books in this field, it falls short in fulfilling any one of its objectives as set out in the preface. As an introduction to plastic surgery, as applied to the face, it contains some excellent sections on principles of technique and design, but the novice would be entirely misled by details and illustrations of methods used in gross and uncommon types of lesion, for there is an over-emphasis throughout the book on the extreme and the spectacular, especially of wartime mutilation. Those experienced in this work should certainly have this book as a reference in view of the obvious weight of experience behind it, but they would find much of the text and illustration redundant. It is a great pity these two main purposes could not be separated and arranged in two separate volumes.

Perhaps the book is mistitled. In many of its sections there are descriptions of procedures for which injury, though not an impossible indication, is certainly most improbable. It is stretching the indications of surgery of facial injury to include under this title details such as the Abbe operation for upper lip defects and some of the nasal plastic procedures which are included. Such redundancy detracts from the practical value of a book of this title.

The first chapter on detailed morphology of facial skeleton and soft tissues seems unnecessary in such detail and the second chapter on wound healing, though in itself probably the best section in the book, would serve better purpose in a general surgical text-book.

The well-illustrated and detailed chapter on fractures includes bizarre combinations of splinting and osseous wiring and other methods generally considered outmoded. This chapter does not match up to some of the standards of British text-books on this subject because of its unbalance by indiscriminate inclusion of the rare and the odd method, with again an over-emphasis on gross destructive injuries. Yet, subcondylar fractures, an important problem in civilian practice, are dismissed too easily as presenting no problems of treatment or complications. The chapter further on in the book on temporo-mandibular ankylosis, however, would suggest otherwise.

In a book of this type there should be no place for details of a technique of such a hazardous and doubtful indication as total reconstruction of an ear by an untried or unproven method merely for "its future possible use".

The book is recommended rather to the discriminative interest of those experienced in this work than to those seeking introduction to the principles and practice of plastic surgery of the face.

[1] "The Surgical Treatment of Facial Injuries", by Varaztad Hovhannes Kazanjian, M.D., D.M.D., and John Marquis Converse, M.D.; 1949. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson. 10" × 7", pp. 586, with 746 illustrations. Price: £5 7s. 6d.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Chronic Carbon Monoxide Poisoning: A Study in Occupational Medicine, with a Danish Summary", by Aage Grut; 1949. Copenhagen: Ejnar Munksgaard. 9½" × 6", pp. 230. Price: 12s.

A study aimed at finding out whether—and if so, how frequently—a syndrome corresponding to earlier descriptions occurs among workers exposed to carbon monoxide.

"Analgesia for Normal Childbirth", by E. H. Seward, M.A., B.M., B.Ch. (Oxon.), D.A., D.Obst., R.C.O.G.; 1950. Oxford: Blackwell Scientific Publications. 8½" × 5½", pp. 30, with illustrations. Price: 2s.

Intended primarily for midwives.

"A Text-Book of X-Ray Diagnosis by British Authors", in four volumes, edited by S. Cochrane Shanks, M.D., F.R.C.P., F.F.R., and Peter Kerley, M.D., F.R.C.P., F.F.R., D.M.R.E.; Second Edition, Volume III; 1950. London: H. K. Lewis and Company, Limited. 9¼" × 6½", pp. 846, with 694 illustrations. Price: 70s. net.

This volume deals with the alimentary tract, the biliary tract, the abdomen, obstetrics and gynæcology and the urinary tract.

"The Urinary Function of the Kidney", by A. V. Wolf, Ph.D.; 1950. New York: Grune and Stratton, Incorporated. 9" × 6", pp. 378, with 49 illustrations. Price: $7.50.

A consideration of renal physiology from the point of view that emphasizes regulation rather than excretion; with an extensive bibliography.

"A Text-Book of Venereal Diseases", by R. R. Willcox; 1950. London: William Heinemann (Medical Books), Limited. 8½" × 5½", pp. 440, with many illustrations, some of them coloured. Price: 32s. 6d.

A text-book with "a global outlook" designed to meet the needs of those treating venereal diseases in all parts of the world.

"Simmonds' Disease: Extreme Insufficiency of the Adenohypophysis", by R. F. Farquharson, M.B., F.R.C.P. (C.); 1950. Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications, Limited. 8½" × 5½", pp. 94, with illustrations. Price: 15s.

A short monograph presenting the clinical and pathological picture of the syndrome.

"Fainting: Physiological and Psychological Considerations", by George L. Engel, M.D.; 1950. Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications, Limited. 8½" × 5½", pp. 152. Price: 20s.

An attempt to understand the mechanisms and clinical characteristics of the various types of fainting and to present the subject in a form useful to the practising doctor.

"Soviet Psychiatry", by Joseph Wortis, M.D.; 1950. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9" × 6", pp. 332. Price: 53s. 9d.

Drawn mainly from a compilation of over 7000 abstracted and digested items from the neuropsychiatric literature.

"The Closed Treatment of Common Fractures", by John Charnley, B.Sc., M.B., F.R.C.S.; 1950. Edinburgh: E. and S. Livingstone, Limited. 9¾" × 7", pp. 202, with 133 illustrations. Price: 35s.

Written primarily for the resident casualty surgeon.

"Recent Advances in Ocular Prosthesis", by J. H. Prince, F.B.O.A., F.S.M.C., F.R.M.S., F.Z.S.; 1950. Edinburgh: E. and S. Livingstone, Limited. 8½" × 5½", pp. 164, with 89 illustrations. Price: 20s.

A companion volume to the author's book "Ocular Prosthesis".

"Emergencies in Medical Practice", edited by C. Allan Birch, M.D., F.R.C.P.; Second Edition; 1950. Edinburgh: E. and S. Livingstone, Limited. 8½" × 5", pp. 576, with 131 illustrations, some of them coloured. Price: 27s. 6d.

Each chapter has been revised and four new chapters have been added relating to skin diseases, eye diseases, anæsthesia and the post-operative state.

The Medical Journal of Australia

SATURDAY, OCTOBER 14, 1950.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

THE OTO-LARYNGOLOGICAL SOCIETY OF AUSTRALIA (BRITISH MEDICAL ASSOCIATION).

THE ear, nose and throat surgeons of Australia have followed the example of other specialists and have formed an Australia-wide society. The idea of the formation of such a body had been entertained for some considerable time, but it was not until the Australasian Medical Congress met in Brisbane last June that it was put into effect. It was first put forward in 1948 when the congress met at Perth. At the preliminary discussions it was decided that the Ear, Nose and Throat Section of the New South Wales Branch of the British Medical Association should proceed with plans for the formation of an all-Australia body so that the inaugural meeting could be held at Brisbane in 1950 when the seventh session of congress was held in that city. Though the members of the new body have made no efforts to draw the attention of the rest of the profession to their venture, the details should be recorded because of the care with which plans were made—plans for the smooth working of the body itself and for its complete dovetailing into the structure of the British Medical Association.

Before a "Special Group" can be formed within the fabric of the British Medical Association in Australia the approval of the Federal Council must be obtained. This was done and the fact has already been recorded in this journal. The name chosen is the Oto-Laryngological Society of Australia—the "Rhino" part of the specialty has been omitted no doubt for reasons of euphony. The objects of the Society are the following:

1. The cultivation and promotion of oto-laryngology and related sciences by all or any of the following:
   - (a) The periodical meetings of members.
   - (b) The collection and dissemination by or amongst members of the medical profession of scientific knowledge and the publication of articles relating to oto-laryngology and the scientific proceedings of meetings.
   - (c) The promotion of research in oto-laryngology with or without grants of sums of money out of funds donated for that purpose.
   - (d) The establishment and maintenance of oto-laryngological libraries and oto-laryngological museums of normal and pathological anatomy.
   - (e) The establishment of prizes for the encouragement of scientific oto-laryngological work out of the funds of the Society or out of funds donated for that purpose.
   - (f) The arrangement of visits by oto-laryngologists from abroad for the purpose of giving lectures and demonstrations.
2. To confer, cooperate and affiliate with other bodies having altogether or in part similar objects within the Commonwealth of Australia or elsewhere.
3. To provide an authoritative body of opinion on matters concerning hearing and to promote the auditory health of and to prevent deafness in the community.
4. To make representations through the Federal Council of the British Medical Association in Australia to the legislature and public officials and others on matters affecting the health of the community and the interests of members.

All members of the British Medical Association in Australia who specialize in oto-laryngology and whose qualifications are satisfactory to the Council of the Society are eligible as ordinary members. After certain requirements have been met candidates for membership are elected by a majority of the Council. The Council consists of the President, the Vice-President, and one representative from each of the States of the Commonwealth. It has been decided that meetings of the Society shall be held at the time of each session of the Australasian Medical Congress and in the city where the congress is to meet. For this reason the office-bearers will come from the State in which the congress subsequent to the election of such office-bearers is to be held. Thus the President elected at Brisbane is Dr. G. C. Scantlebury, of Melbourne, and the eighth session of congress is to be held at Melbourne in 1952. It is to be noted that the Society will hold a scientific meeting at least once a year independently of or in conjunction with any State sectional meeting or meeting of any organized body of oto-laryngologists in a State where no section of the Society exists. Any member of the British Medical Association may attend a scientific meeting of the Society on being introduced by a member of the Society subject to the discretion of the chairman.

Two things remain to be done. The first is to congratulate the oto-rhino-laryngologists of the several States for having formed a society within the framework of the British Medical Association. The second is to express the hope that the Society will prosper and fulfil the expectations of its members.

MEDICAL ADVERTISING.

THE American Medical Association very wisely takes a firm stand on the matter of advertisements. A reminder of its policy has been recently issued,[1] with a warning that the policy will be enforced. Included among the advertising rules of the Association are the following:

> Advertisements will not be accepted which, either by intent or inference, would result in deceiving, defrauding or misleading the reader. . . . If testimonials or quotations appear in advertising the validity of the claims made and the probable import on the reader will be subject to critical appraisal before acceptance. . . . Quotations or excerpts from published papers are not accepted if by themselves they distort the true meaning

[1] *The Journal of the American Medical Association*, March 18, 1950.

intended by the authors or are otherwise misleading. Quotations from the Association's publications may be used in advertisements only with express permission in each instance.

The warning issued applies particularly to the unauthorized use in advertisements of references to and quotations from the Association's publications. As is pointed out, when references are designed to attract the attention of qualified readers and consist of factual unbiased presentations they can serve a useful purpose; the position is otherwise with "advertisements for products whose usefulness is questionable, firms whose integrity is in doubt or products that are promoted for sale to the laity". The Association naturally objects to being a party to false advertising, especially if it includes the implied endorsement of product or claim on the part of one of the Association's publications. All reputable medical journals will agree with these views, and THE MEDICAL JOURNAL OF AUSTRALIA will follow the lead of the American Medical Association in this matter. All advertisements offered for publication in this journal are submitted to close scrutiny. Every effort is made to eliminate extravagant statements, claims of superiority over other products and misleading use of quotations or references; this journal also declines to accept advertisements mentioning unethical products or submitted by firms or individuals whose integrity is not fully established. This means that the journal attempts as far as possible to stand behind the claims made by an advertiser. Products which have been accepted for advertisement by the *British Medical Journal* and those approved by the Council on Pharmacy and Chemistry of the American Medical Association are accepted without question. Other products, particularly those manufactured in Australia, are investigated with care from all points of view. Such a guarded attitude towards unethical products and doubtful advertisers will no doubt be readily appreciated, but it may be as well also to remind enthusiastic writers of copy for ethical products that lack of discretion may do disservice to a perfectly good product; we would endorse the view of *The Journal of the American Medical Association*: "If a product cannot be sold without untruthful or misleading statements, it probably is not worthy of much attention by anyone."

Current Comment.

RESULTS OF TREATMENT OF MILIARY AND MENINGEAL TUBERCULOSIS WITH STREPTOMYCIN.

STREPTOMYCIN has rescued many patients with certain forms of tuberculous infection, but their after history has not yet been fully worked out. A year ago Paul Bunn published a report of the results of treatment of 100 patients suffering from miliary and meningeal forms of tuberculosis; the series was unselected, the cases being consecutive, and therefore represented a fair cross-section, if it is assumed that correct criteria were adopted in their selection for this form of treatment. At that time 24 only of the original patients were living. Bunn now presents the results of a further follow-up of the survivors at the twelve-monthly period, who have been under observation for an average period of practically two years.[1] During the past year four patients have died, and two others are in the terminal stages of tuberculosis. The causes of death were relapse of tuberculous meningitis, recrudescence of miliary and disseminated disease, and, in one instance, intercurrent disease. One of these patients has had a notably long history, and though still surviving at the time of report, had a severe and unresponsive form of meningeal infection which recurred fourteen months after the termination of a course of streptomycin. Seventy-nine of the 100 patients have thus succumbed to an illness which was tuberculous in every instance but one, and which was of miliary or meningeal nature. The author points out justly that the results of such a series are more impressive if those patients are excluded who died within a fortnight of the start of treatment. No less than 23 patients in this series died within this period, and most of these showed either no response to the drug, or only an evanescent improvement. All those who survived this early period showed improvement, though this was not always sustained for one reason or another. Remission was only temporary in the case of 32 patients, and death followed after 30 to 120 days in spite of continued therapy. Twenty-four patients died after the fourth month of treatment, but the longer an individual survived the greater was his chance of apparent arrest of the disease or cure. Even some of the most encouraging results, with an impressive degree of response to streptomycin, were, however, not sustained for longer than a period varying from one to eighteen months after treatment began. Of the survivors after two years only one had signs of progressive disease, but at least seven are known to have an active focus in the skin, in bone or in the lungs. Fourteen patients have been observed in whom active foci became quiescent during treatment.

These results are encouraging up to a certain point. The author points out frankly that insufficient information has been gained from autopsies, and states that if streptomycin is to be used effectively, more such knowledge will be necessary. Miliary tuberculosis in this series bears a better prognosis than the meningeal type, and a combination of the two is still more lethal than either. This, of course, we knew long before streptomycin was discovered. The greater survival rate of patients with miliary disease has confronted them with the greater risk of the meningeal form; Bunn's series shows that two-thirds of the survivors from miliary tuberculosis will later show evidence of meningeal infection. He suggests that early diagnosis would be assisted by routine periodical performance of lumbar puncture. Two years appears to be the smallest period of time in which really useful prognostic ideas can be gathered, and, as shown above, the real value of the drug appears only if the rapidly fatal cases are removed from the statistical survey. Two other interesting points may be noted. The live pathology of tuberculosis of the meninges now follows the pattern described by Rich and McCordock a number of years ago, on the evidence of morbid anatomy, once again emphasizing the value of the autopsy. Also, the limitations of streptomycin are thrown into relief by these very observations, for it appears that, as has been shown in the literature, adjuvants such as lysins, anticoagulants and accessory antibacterial drugs may yield better results than those possible from an antibiotic alone. It is to be hoped that heed will be paid to the recent warnings against indiscriminate use of an agent which needs not only careful use, but careful appraisal.

[1] *The American Journal of the Medical Sciences*, February, 1950.

CHRONIC FAILURE OF THE BONE MARROW.

FOR a number of years confusing clinical pictures have been described which have not always been clarified by attempts to explain them. This general statement may well be true in many branches of medicine, but it applies with especial force to certain states in which abnormalities are found in the liver, spleen, circulating blood and bone marrow, and also to sclerotic changes in the bones. John P. Wyatt and Sheldon C. Sommers, in presenting a study of a series of 30 cases of this syndrome of chronic marrow

failure, myelosclerosis and extramedullary hæmopoiesis, attempt to classify them from a pathological standpoint, and suggest possible ætiological causes.[1] They summarize the morphology of this condition as follows: (*a*) necrosis of semi-mature erythroid and myeloid marrow cells; (*b*) reactive overgrowth of the remaining cells, usually of a more immature type; (*c*) hæmopoiesis in tissues outside the marrow; (*d*) relative unaffection of reticulum and stroma cells, but later overgrowth of these; and (*e*) suggestive features in the case histories pointing to the possibility of toxic agencies such as have been suspected previously in so-called refractory anæmias. In other words, in their work they attempt to approach ætiology of an obscure group of diseases affecting the blood-forming organs from the viewpoint of pathology, and to separate off a subgroup which may shed some light on the whole subject. They remark that cases were reported in the literature in earlier days, and classified as leuchæmia simply on the grounds of an increase in white cells in the circulating blood and the presence of immature cells. Cases with leuchæmic marrow and myelosclerosis not attributed to radiation have also been described, but till recent years no attempt seems to have been made to place them in some degree of order. The literature has been loaded with an increasing number of names, whose chief function has been to call attention to the condition. The authors describe the changes in the marrow characteristic of clinical myeloid metaplasia, and contrast these with the findings in disseminated carcinoma which has a predilection for the bone marrow. They point out that occasionally hyperplastic changes are found, with perhaps scattered foci of red or yellow marrow, and density of the bones with thickening of the cortex. Both erythroblastic and myeloblastic overgrowth appear, and sometimes undifferentiated stem cells. They mention particularly what they call "blighted" cells, some of which cannot be distinguished in species with any certainty. This picture is replaced later in the disease by atrophy of the marrow, and the scattered foci become devoid of hæmopoietic cells. The end stage may sometimes assume the appearance of a "fretwork" osteosclerosis. In the spleen and liver extramedullary hæmopoiesis is well marked, though less conspicuous in the latter. As time goes on an increasing number of immature cells are seen. Lymph nodes, though not usually conspicuously enlarged, show some evidences of blood formation also.

Wyatt and Sommers have found in the literature 129 cases which fulfil the criteria they lay down, and they think that there are many others, though not critically acceptable. They analyse their own cases, and point out that four patients gave a history of prolonged exposure to benzol. Others had used paint removers, and six were later found to have had industrial exposure to industrial solvents. In radium poisoning, such as the well-known variety found in workers painting watch and clock dials with radium paint, the sequence of hyperplasia and replacement sclerosis has also been found, and the authors consider that the findings are identical with their own in cases of diverse ætiology. Reverting to this series of 30 cases, we note that five patients had histories of exposure to extrinsic toxic chemicals, such as weight-reducing pills, insect sprays, paint removers and various pharmaceutical products, but the evidence is merely suggestive, and no detailed studies were made. Wyatt and Sommers base their findings on a good stratum of morphology, as there were twenty autopsies performed in their series. They conclude that the changes may be briefly described as a repeated necrobiosis of maturing hæmopoietic cells, followed by a reticular overgrowth in the bone marrow, and in many instances, ossification. They have gone into the question of endocrine factors also, and feel that these may be of significance, as well as dysfunction of the liver, and cardio-vascular disease. However, the most valuable conclusion is that there seems some justification to suspect the pathogenetic importance of protracted exposure of the bone marrow to certain substances which normally are conjugated in the liver and excreted. If chronic failure of the bone marrow is suspected it will be seen that radiation and splenectomy are contraindicated.

[1] *Blood*, April, 1950.

THE PREVENTION OF SUNBURN.

THE season of sunburn is here again, and protection is sought both by those who feel compelled to expose a normal skin to the sun for a long time and by those whose sensitive skins are disturbed by minimal exposure. Brian Russell and Daphne Anderson[1] point out that the prevention of sunburn in a member of the first group is simpler than the protection of a light-sensitized person; the one has a healthy skin and the other a skin already affected in some way, so that often he is less tolerant than the normal person of the local application of chemicals as well as of sunlight. Especially when prescribing for lesions already present, the medical attendant should warn the patient that he cannot foretell whether or not a preparation will be tolerated and that trial-and-error methods are necessary. Russell and Anderson have carried out tests with a series of screening agents incorporated in different bases, having as their subject a patient with *eczema solare*, apparently due to the light within the sunburn spectrum range. At the same time they have determined the absorption spectra of various combinations of bases and chemical screens for comparison with the clinical findings. They have concluded that protection against the sunburn spectrum is provided by a base of vanishing-cream type containing one or other of the following agents: tannic acid 5%, quinine hydrochloride 5%, pyribenzamine 5%, sodium *p*-aminobenzoate 10%, salol 10%, or yellow soft paraffin 50%. Any one of these creams may be used to prevent sunburn, but that containing tannic acid is the first choice. However, when the substances are used in the treatment of light-activated diseases, a watch must be kept for skin intolerance to the light-screening active principle itself or to some component of the base. Of the substances in the list quoted, tannic acid is the most innocuous, followed by salol, sodium *p*-aminobenzoate, pyribenzamine and quinine. Sodium *p*-aminobenzoate should not be used if there has previously been sensitization to sulphonamides or benzocaine. Certain points are important about the bases that may be used. Yellow soft paraffin is an effective screening agent when added to creams in proportions of 50% or more, but it is cosmetically unsatisfactory and its occlusive and "heating" properties may cause discomfort; in proportions of 25% and less it does not act as a screen, but, on the contrary, has an intensifying effect in the sunburn spectral range. Apart from its own screening qualities, the base used influences the efficacy of the light-screening agents, for example, by its emulsifying properties, and so must be chosen with care. The vanishing-cream type of base is both effective and of good cosmetic quality. Russell and Anderson found the following prescription for a base satisfactory apart from the occasional instance of intolerance to triethanolamine: stearin 25 parts, triethanolamine 1 part, glycerin 10 parts, oil of theobroma 1 part, cetyl alcohol 0·5 part, distilled water 62·5 parts (to be dispensed in an airtight container). A special problem exists in the more unusual cases of sensitization to the longer visible wave-lengths in the violet-blue range of the spectrum (the wave-lengths usually involved are in the ultra-violet range between 2900 and 3300 Å); the screening agents already mentioned are ineffective in these cases, and physical agents are used, such as calamine, zinc oxide, bentonite and titanium dioxide, though with less success. Fortunately these last-mentioned conditions are rare, and for most people reasonably satisfactory protection is possible. However, the use of protective agents may usefully be supplemented by moderation in exposure to our hot Australian sun.

[1] *The Lancet*, August 12, 1950.

Abstracts from Medical Literature.

DERMATOLOGY.

Psoriasis.

B. RUSSELL (*The Practitioner*, March, 1950) states that, according to Cockayne, the latent inherited predisposition to psoriasis occurs as a complete and regular dominance; but it often remains dormant throughout life, so that on the average only about one-fifth of a psoriatic subject's children will ever show the condition and a little over one-eighth of the grandchildren. Various stimuli may raise latent psoriasis to the clinical flood level. The stimuli may operate at any time of life. Often it is only when two or more types of disturbance —infective, physical, endocrine, metabolic, emotional—happen to coincide that psoriasis results. If the family incidence is slight or non-apparent, psoriasis is more likely to have been precipitated by a severe emotional conflict or infection. The conception of varying depths of latency is useful in deciding what treatment is necessary or likely to succeed in any one patient. The fundamental cause of psoriasis remains obscure. The stimuli that most commonly seem to activate or aggravate it include physical injuries to the skin, infections and emotional upsets causing lowering of mood. The skin is not only the physico-chemical barrier against injury, but also the sense organ for the initiation of autonomic adjustments to pleasant or unpleasant surroundings, whether they be physical or personal. The psoriatic needs protection against cold, damp, dark, and injury, but he also needs a happy personal environment. If the skin condition is related to the emotional turmoil of an unresolved conflict, elevation of the spirits and the abatement of the psoriasis can be brought about only by emotional readjustment and resultant peace of mind. The greatest disservice to a psoriatic is to give him a month's supply of ointment with the remark that "psoriasis is incurable". The author discusses different clinical types of psoriasis and various details of treatment.

Emotion and Disorders of the Skin.

O. SPURGEON ENGLISH (*Archives of Dermatology and Syphilology*, December, 1949) states that most, if not all, dermatologists accept the fact that emotion plays a role in disorders of the skin. The most commonly encountered emotions are the need for love, anxiety, hostility, inferiority feelings, ambivalence, guilt, ambition and envy. Since emotions will find expression in any or all parts of the body, it is inevitable that so important an organ as the skin should be affected. The author describes how the emotions affect the skin. Emotion may seem slower to appear in the skin than in the heart or the gastro-intestinal tract, but in blushing and sweating we have very prompt phenomena, which sometimes are distressing to a repressive patient. Also, urticaria and allergic phenomena have a high incidence and can make their appearance quickly. Dermatology and psychiatry share the phenomenon of having a few acute conditions and many which are slow to improve. The skin is like other organs in that it may symbolically represent an inner attitude. In addition to "burning with shame", it may weep out of sadness. The author enumerates the emotions, in a general way indicates their mode of action, and describes the emotional states in which are encountered a linking of emotions and skin problems. He then discusses neurotic excoriation, *dermatitis factitia* and emotions and skin sensitivity. He states that there is increasing evidence that maternal rejection plays a large role in psychosomatic conditions, just as in neuroses and psychoses. Frequently inflammation, itching and weeping of the skin in eczema are observed when the patient is going through some environmental stress which places him in a position of responsibility where he feels alone and unprotected. *Pruritus ani* and *pruritus vulvæ* are not always of psychological origin, but a psychological factor plays a contributing role in many cases. Cancer phobia and syphilophobia are psychiatric, not cutaneous, conditions. Trichotillomania is not a condition of the skin, but a piece of neurotic behaviour. What one sees in the hairy regions are the end results of a compulsion to extract hairs forcibly with the fingers. This unusual behaviour starts as a perverse means of gratification in the production of pleasurable pain. Hyperhidrosis, with sweating of the hands, axillæ and feet, is fairly common; there is considerable evidence that it is entirely emotionally conditioned. Urticaria is one of the conditions of the skin for which an emotional factor has been noted and accepted for some time. The author quotes Ingram, who called attention to the emotional instability of those suffering from seborrhœic dermatitis by stating that it could vary from the sullen, sulky indolence of patients who present some of the heavier forms of acne to the high-strung overactivity of the patient with rosacea. The author considers that as the role of emotions in cutaneous conditions becomes more widely accepted, we shall have more psychotherapeutic efforts and hence more reports of results of treatment; as things stand the patient still has too little faith in what can be done for his condition by a psychotherapeutic approach.

Contact Dermatitis.

H. R. VICKERS (*The Practitioner*, March, 1950) states that contact dermatitis, as the name implies, is that type of dermatitis which occurs when harmful agents attack the skin. It can be divided into traumatic and sensitization types. The traumatic type is that produced by contact with some substance which would evoke a similar reaction in the skin of any other average individual; the sensitization type is that produced by contact with a substance to which the skin cells of the patient have become specifically sensitized and which does not produce dermatitis in an average normal person. Traumatic dermatitis is relatively uncommon; it normally affects washerwomen, machinists in contact with cutting oil, cement workers and miners. Sensitization dermatitis is much more common. When epidermal cells become sensitized the following factors appear to play a part: (i) idiosyncrasy of the individual cells, (ii) contact with sensitizing substances and (iii) the age of the patient. As sensitization is not common in children, the author considers that some hormonal influence occurring at puberty is also necessary for the establishment of sensitivity. When sensitization occurs the whole of the skin is affected, and any part of the skin which comes in contact with the substance will react by developing dermatitis; in severe cases a minute amount of the substance absorbed through the skin, and entering the blood-stream, will produce a "secondary sensitization dermatitis" in any area with which it comes in contact. It is because of this generalized sensitivity of the skin cells that the patch test is of such value in elucidating the cause in these cases. Common causes of sensitization are plants, medicaments applied to the skin, cosmetics and articles of clothing. Medicaments applied to the skin are an increasing cause of sensitization dermatitis. Sulphonamides are the worst offenders and the most dangerous. They may not only cause the development of sensitivity with serious, even fatal, results, but also render the skin more susceptible to the action of light. They should never be used locally in the treatment of skin disease. Penicillin cream and ointment are also giving rise to dermatitis. Other applications commonly causing trouble are mercury, flavine, picric acid, and various proprietary ointments containing local anæsthetics. Cosmetics are frequent offenders. Accurate and careful history-taking is of the greatest importance in diagnosis. Particular attention should be paid to the site of the first-noticed eruption and the time relationship between contact with a possible irritant and the onset of the rash. The diagnosis is confirmed by patch tests, but in acute cases it is necessary to wait till the rash is subsiding before applying the test; otherwise the original rash may be aggravated. For local treatment the blandest substances should be used.

Hormonal Therapy of Acne Vulgaris.

W. H. GOECKERMAN (*Archives of Dermatology and Syphilology*, February, 1950) considers that if the proper hormonal preparation could be obtained it should beneficially affect the process in acne. He therefore experimented with desoxycorticosterone and antuitrin (unfractionated anterior pituitary lobe extract), only to be disappointed with these preparations. In 1940 he decided to treat all female patients with œstrogens. Both natural and synthetic preparations were administered, sometimes individually and sometimes in combination. At no time was the patient permitted to become uncomfortable. The dose was adjusted to the requirements of the individual. The author states that a combination of the natural and synthetic œstrogens is the best, although synthetic œstrogen alone is often effective.

Partial Alopecia due to Scalp Massage.

R. E. BOWERS (*The British Journal of Dermatology and Syphilis*, June, 1950) states that observation of normal infants shows that the constant friction of the head on the pillow can produce a patch of short hair on the occiput; the patch grows in a normal way soon after the infant begins to sit up. In view of the frequency with which massage of the scalp is urged

with various preparations, the author believes that a similar appearance can occur in adults. He quotes six cases in detail and mentions the following features: (*a*) The patient complains of patchy baldness of more or less gradual onset, and the affected site is covered with short, lustreless, brittle and sometimes twisted hairs. (*b*) The hairs may be firmly fixed in the scalp, but sometimes come out very easily if pulled. (*c*) The affected hairs are broken off, and beneath the microscope the ends appear frayed as in *trichorrhexis nodosa*. In one case a bush-like node was seen on the shaft. The underlying scalp may be normal, or may be reddened by friction. (*d*) The condition is rapidly restored to normal if massage is discontinued. (*e*) The patients were questioned on the type of lotion which had been applied to the scalp; none were considered to be contributary. The author states that the evidence makes it probable that massage can cause a form of baldness which has certain characteristics. He suggests that massage is a cause of some cases reported as *trichorrhexis nodosa* and *fragilitas crinium*.

UROLOGY.

Squamous-Cell Carcinoma of the Renal Pelvis.

H. Q. GAHAGAN AND W. K. REED (*The Journal of Urology*, August, 1949) describe a recent personal case of squamous-cell carcinoma of the renal pelvis and add two other cases culled from the records of their hospital. A review of the literature reveals that only 106 cases have been described to date. The incidence of this condition is found to be about the same as to sex and side. It is most common in the fifth and sixth decades of life. A correct pre-operative diagnosis has never been made. Infection is present in most instances, and renal calculus is associated in nearly 50% of the cases. Nephrectomy is the only treatment. The prognosis is poor and no five-year cures have been reported.

Streptomycin in Genito-Urinary Tuberculosis.

J. K. LATTIMER, J. B. AMBERSON AND S. BRAHM (*The Journal of Urology*, December, 1949) report from the Veterans Administration on 253 cases of genito-urinary tuberculosis in which treatment was with streptomycin alone. They state that as a result of this experience, some generalizations can be made about optimum dosage and limitations of this drug. It is considered that, when active tuberculosis is found in one kidney, it must be suspected that there are dormant tubercles in the other kidney, which may later become active if resistance is lowered. The most effective dosage regimen against active ulcerating renal lesions, when streptomycin alone was used, was 0·3 gramme given every four hours day and night for one hundred and twenty days. As the dosage and time of treatment were lessened, the effectiveness decreased. Forty-two day regimens were inadequate. Large renal lesions responded poorly. Any lesion that was visible in the pyelogram probably contained necrotic and fibrous tissue and was classified as a "large renal lesion". It has now been decided that surgery is preferable in such cases if the active disease is unilateral. Small renal lesions, with no visible pyelographic change, although tubercle bacilli were in the urine from that kidney, responded well. Superficial ulceration and œdema of the bladder responded well to streptomycin treatment. However, contracted bladders and ureteric strictures due to deep-seated fibrous lesions did not improve. Epididymal tuberculosis is better treated by surgery, followed by three weeks of streptomycin therapy. Prostatic tuberculosis did not respond well, except when severe cystitis resulted from local extension of the lesion. The chief limitations are the development of resistance and the presence of necrotic, caseous or fibrous tissue. Combined therapy with streptomycin and PAS (para-amino salicylic acid) is now under investigation and appears promising.

T. R. HUFFINES AND W. D. WEBER (*The Journal of Urology*, December, 1949) give their experience with 59 cases of genito-urinary tuberculosis in which streptomycin therapy was used. They have been able to bring about at least temporary arrest of the disease, with obvious immediate benefit, in 82% of their patients. They have been able also to perform operations on patients who would have been abandoned surgically. They state, however, that streptomycin is by no means the last word on the subject. The human body can kill the tubercle bacillus under favourable conditions and if given enough time. Perhaps the desired answer will be in the form of a drug that will hold the tuberculous process in check while the body destroys the organisms themselves. At a recent meeting of the Streptomycin Committee in Chicago, it was noted that the tubercle bacillus tended to show resistance to therapy about the forty-fifth day. It was thereupon decided to reduce the duration of streptomycin treatment to six weeks, instead of four months as formerly.

Interstitial Cystitis.

J. A. SEAMAN (*The Journal of Urology*, January, 1950) describes the basic syndrome of interstitial cystitis as (i) excruciating pain in the vesical region, (ii) relentless frequency of micturition day and night, (iii) often urgency of micturition to the point of incontinence and (iv) clear urine which is often sterile. The author has never seen the disease in the male, and states that in females it is usually the middle-aged who suffer. The disease has had over two dozen names, the most common being Hunner's ulcer, after G. L. Hunner, who described it in 1914. Many hundreds of cases have been reported by careful observers, and much experimental work has been done, but just when it seems that the problem is solved the elusive cause escapes. The typical lesion has the appearance of submucous fibrosis arranged in octopus fashion, with the tentacles, thick or thin, extending irregularly outward from the centre, which may be no bigger than a few millimetres. The tentacles vary in length up to several centimetres. Sometimes it seems as if the bands of scar tissue are actually lifting up the mucous membrane. Intercurrent cystitis may mask the lesion by making the whole area red. After the temporary infection has been conquered the lesion may be studied endoscopically under anæsthesia. As the bladder slowly fills up to its poor capacity of three to five ounces, little beads of blood appear along the line of the fibrous bands as they are stretched. Microscopically there is the appearance of inflammation and fibrosis submucosally in the affected area. Under this round-cell infiltration is seen in varying degrees extending through the muscular wall. Capillaries and venules are dilated and there is leucocytic infiltration of nerve sheaths. Tissue staining has failed to demonstrate any organisms. Treatment in the past has been of manifold types from endovesical fulguration to transplantation of the ureter into the bowel. The author considers that not enough attention has been paid to endocervicitis as a form of infection; this should always be searched for, and treated if this is indicated. Endoscopically one can perform a useful operation by careful transverse incision of the tentacle-like bands with a needle electrode. This allows the irrigating fluid to distend the organ a little more. Gentle daily distension for a week before the patient leaves hospital will often relieve the patient for several years. In the worst cases, lasting for years with regular recurrences in spite of repeated treatment, diversion of the urine is the only recourse.

Bilateral Renal Hypernephroma.

M. K. BAILEY AND V. H. YOUNGBLOOD (*The Journal of Urology*, April, 1950) state that the occurrence of bilateral hypernephroma (clear-cell carcinoma) of the kidney is quite rare, only 11 cases having been reported in the English language. Most of the cases reported relate to simultaneous bilateral occurrence, usually with a large neoplasm in one kidney and a small one in the other, with or without metastasis elsewhere in the body. It may be, in such cases, that each is a primary growth, or one may be a metastasis of the other. There is no way of proving it either way. The authors report a recent personal case in which there was no evidence of metastasis in other parts of the body. In this case the tumour causing death was of lower malignancy histologically than the other. It is assumed therefore that each renal neoplasm was primary in itself. In all the 12 reported cases the patients were males.

Dorso-Lumbar Approach to the Kidney and Adrenal.

G. NAGAMATSU (*The Journal of Urology*, April, 1950) has designed a way of approaching the renal and suprarenal fossæ from above by an extrapleural and extraperitoneal route. Removal of short segments of the lower three ribs, at a point a little distance behind their angles, results in the formation of a retractable osteoplastic flap of the otherwise rigid lower part of the thoracic cage. The advantages of this exposure are (i) that tumours in the renal and adrenal regions may be operated on with primary handling of their vascular supply, (ii) that high, fixed, infected kidneys can be removed with minimum risk to the important nearby structures, and without contamination of the pleural or peritoneal cavity, and (iii) that secondary nephrectomies lend themselves to easier handling when approach is through previously untouched tissues well above the primary incision.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held on April 5, 1950, in the Medical Society Hall, East Melbourne, DR. ROBERT SOUTHBY, the President, in the chair.

Gastric Biopsy in Pernicious Anæmia.

A paper by DR. R. K. DOIG and DR. IAN WOOD, entitled "Gastric Biopsy in Pernicious Anæmia", was presented (see page 565).

DR. REGINALD MOTTERAM said that Dr. Wood was to be congratulated on conceiving the idea of performing gastric biopsy on the patients. He believed that courage was needed to carry out an investigation of the kind reported to them that night; perhaps its greatest contribution was in putting the interpretation of test meals on a sound histological basis and establishing an exact co-relationship between them. He added that the work had shown that the secretion of the gastric mucosa could not be increased in conditions such as chronic gastritis. In conclusion, Dr. Motteram said that he had been very happy to have the opportunity to be associated with Dr. Wood and their fellow workers in the initial stages of the particular project under discussion.

Dr. D. B. ROSENTHAL, after thanking Dr. Wood for assisting him in the solution of certain clinical problems, asked whether it was known at what stage in life pernicious anæmia developed as a clinical entity; he had wondered whether it was a congenital condition and whether its origins could be recognized.

DR. PETER PARSONS said that he wished to congratulate not only the speakers but the technicians who had had to cut the sections from the fragments obtained with the instrument Dr. Wood had shown them. He stated that he had seen the work started and would like to know whether the technique, which did not seem to be hazardous, had been developed to the point at which it could safely be used in the out-patient department. Bleeding did not appear to be a serious complication, but occasionally large superficial vessels would be encountered and might produce profuse bleeding from superficial ulceration; he would like to know whether those vessels were avoided in taking samples. He pointed out that the end of the instrument always rested close along the line of the greater curvature, and even if a second sample was obtained, it, too, would come from the greater curve; it was assuming a lot to suppose that elsewhere the mucosa would have precisely the same structure and the same lesions; through the gastroscope the appearance varied greatly in different situations. He went on to say that it would be of interest to attempt to correlate biopsy findings with gastroscopic observations and suggested the suitability of the Herman-Taylor gastroscope for the purpose, as the eyepiece could be focused without movement of the instrument off the spot under observation at any given time. Dr. Parsons then asked Dr. Wood whether he had any compunction about using his biopsy instrument on young people with a high acid curve and rapid emptying time who were prone to stoma ulceration after operation; the risk might be a real one. In conclusion, Dr. Parsons expressed the opinion that the instrument was very interesting; some fine results had been obtained, and the histological specimens were excellent. The procedure was definitely a research one, however, and was scarcely likely to be available in general practice; though the removal of the specimen was not very difficult, what was done with it afterwards and the expert interpretation of the sections were critical steps in the procedure, and, in those respects, it was in the same category as the liver biopsy technique. He congratulated all concerned on an interesting and excellent piece of work.

DR. JOHN MCLEAN said that he was very interested in pernicious anæmia, and he considered that the gastric biopsy instrument would be very useful if generally adopted in the special investigation of patients with pernicious anæmia; in many instances the diagnosis had to be in doubt and, especially when the patients had had liver therapy, the hæmatology was somewhat confused; those comments applied also, of course, to early diagnosis of subacute combined degeneration when the blood picture was not convincing. Dr. McLean asked whether the instrument had been used on any patients with Wilkinson's achrestic anæmia.

DR. J. E. SEWELL asked whether any of the cases of atrophic gastritis had been first diagnosed without the aid of gastroscopy; gastroscopy had been said to have been disappointing, but when atrophic gastritis was present it was comparatively easy to see it. He had noted in the slides shown illustrating gastric atrophy that there was variation in the depth and degree of cellular infiltration, but he suspected that that would be the case from place to place and from time to time in the gastric mucosa of any one patient; he felt that it might be going too far to draw conclusions based on histological sections of single specimens obtained at different stages.

DR. J. R. BELL said that with everyone else he shared in the general appreciation of the value of the work initiated by Dr. Wood and demonstrated that evening; he felt that a new conception of the nature of gastritis was needed to restore respectability to that diagnosis which had been lightly and unsatisfactorily made hitherto. Dr. Bell gave a brief history of the changing ideas on gastritis, mentioning the advances made by formalin injection of the stomach, Forcell's work on the radiographic changes of the mucosal folds and, more recently, the introduction by Schindler of the flexible gastroscope. The introduction of the flexible gastroscope had made gastroscopy a comparatively simple procedure, but the interpretation of the observations was by no means simple. The ultimate effect on accuracy of diagnosis was a state of indescribable confusion as in the Tower of Babel; each class of investigator spoke a different tongue, but a universal language and close collaboration of investigators were needed; until that collaboration was practised the diagnosis of gastritis would remain chaotic. He had the feeling that the gastritis of the gastroscopist could not be reconciled with that of the pathologist or with that of the biopsy specialist. He thought that Dr. Wood had rather decried gastroscopy, much in the same way as he (Dr. Bell) had been said to have done, though he had pointed out its great limitations while agreeing with its devotees that it was a very useful procedure. After performing thousands of gastroscopic examinations the younger Chevalier Jackson always freely admitted the difficulties of interpretation; atrophic *versus* hypertrophic gastritis baffled even Chevalier Jackson. Dr. Bell then commented on what Dr. Doig had said about the relief of pain by the use of alkaline powders even when achlorhydria was established. Dr. Bell said that, in his experience, some of the patients had more satisfaction from hydrochloric acid in adequate dosage; the ones with associated diarrhœa had derived benefit from the acid therapy; the relief by alkaline administration might not just depend on the alkaline content, but might be due to some side-effect on muscular tension. In conclusion, Dr. Bell, speaking of the relationship of pernicious anæmia and subacute combined degeneration to underlying achlorhydria, said that he was interested in Dr. Doig's statement that histamine achlorhydria was the common finding; he had believed that for many years. The very close association between pernicious anæmia and subacute combined degeneration had been established originally on the common presence of unalterable achlorhydria.

DR. R. ANDREW said that he, too, felt that the work on gastric biopsy that had been described held great promise and that great courage had been required by those who had gone ahead with the investigation. He would like to know a little more about the work; for instance, the age-grouping mattered, yet perhaps the controls used belonged to an earlier age group and the subjects submitted to biopsy were older; he would like to be told what the experiences had been by age-groupings of the subjects. Then again, there was unquestionably a group of functional diseases at either end of the gastro-intestinal tract, in the investigation of which gastric biopsy was not likely to be of much assistance; but only by its use and by other investigatory methods would all of the cases be sorted. He added that he believed that it was the case that the findings of Herman Taylor and Schindler by gastroscopy were at variance, and that the latter would discover changes in the mucosa the appearances of which would be regarded as normal by the former, being, in reality, due merely to froth and foam on the mucosa and not lesions at all. They must therefore be extremely chary in accepting descriptions that might be ascribable to divots on the fairway but told nothing whatever about the grass itself.

Dr. R. Southby, from the chair, said that he had always been very interested in the question of achlorhydria, especially in infants and young children. The cases could often be picked on the histories and conformed to a series of syndromes by age-groupings. It was amazing how frequently allergy entered the clinical picture and it was by no means uncommon to find allergy, pernicious anæmia and

achlorhydria in the family history affecting the parents or grandparents and apparently transmitted from previous generations. Dr. Southby described a group of babies, ten to twelve months of age, healthy and lusty, but with a lot of diarrhœa of the lienteric type, more than six stools being passed by day and none during the night; on inquiry the mother would be asthmatic or the father taking acid drops. A second group was typified by the pale-looking child of sallow appearance referred from the school as anæmic; on investigation a mild degree of anæmia might be proved, but the tonicity was poor and the response to iron therapy was disappointing until it was reinforced with dilute hydrochloric acid. A third syndrome was less frequently encountered, and the children showing it were older, perhaps eight to ten years of age. The chronic ulcerative colitis label was suggested, and blood and mucus might even be present in the stools, but on investigation no organic lesions of the lower part of the intestinal tract could be established; quite a proportion of those patients responded dramatically when dilute hydrochloric acid was prescribed. Dr. Southby went on to say that there was a dosage difficulty, and he had had to adopt empirical trial and error methods of deciding the dosage in individual cases; the amount of acid secreted in twenty-four hours for normal healthy persons was not apparently known with sufficient precision to act as a basis for rational estimation of dosage. He had started cautiously with five to ten minims three times daily and had gone on increasing the dose until for one little girl he had prescribed 90 minims, three times a day, before she had produced formed stools; later it had taken two drachms, given three times daily, to make her constipated for the first time in her life; the maintenance dosage was ultimately fixed for her at 30 minims three times a day. Finally, Dr. Southby said that he would like to know whether the patients with pernicious anæmia had to take acid for the remainder of their lives.

Dr. Doig, in reply to Dr. Parsons, said that the patients on whom gastric biopsy was performed often were out-patients, who were retained for a short time, from half an hour to two hours, in the out-patient department under observation before going home; only four hæmorrhages had occurred, and only one of them had been worrying, the subject being a man with hypertension who had needed a transfusion of blood. Hypertension itself was not a reason for avoiding the biopsy, but the presence of œsophageal varices and lowered prothrombin level were contraindications until œsophagoscopy and injections of vitamin *K* preparations had minimized the risk. Biopsy with the new instrument and with the technique they had developed was really much less formidable than gastroscopy, and they had not experienced any difficulty in getting the patients to return for repetition of the procedure. The site from which the samples were taken was not so strictly along the greater curvature as might be thought, and it was believed that the changes observed were general rather than local ones in most cases.

In reply to Dr. Rosenthal's question, which he considered extremely apt, Dr. Doig referred Dr. Rosenthal to the symptomatology which Dr. Southby had expounded. He agreed that the biopsy technique was not likely to be available for the everyday investigation of dyspepsia in general practice. He informed Dr. McLean that biopsy had been performed in the presence of varied kinds of anæmia; they had not encountered a real example of achrestic anæmia, but refractory anæmia with histamine-fast achlorhydria was associated with a biopsy specimen having the typical appearances of atrophic gastritis. Dr. Doig, in reply to Dr. Andrew, said that nothing had been specifically planned for the investigation of the functional dyspepsias by gastric biopsy; dyspepsia of unknown or unproven ætiology still remained the largest group. He conceded that the controls used were somewhat younger than the patients with lesions. Finally, holding the views he did, he considered that the amount of hydrochloric acid used therapeutically seemed to be a futile question; but he agreed that from the clinical point of view it was often otherwise.

Dr. Wood expressed deep appreciation of the discussion and took the opportunity to thank all those who had helped and encouraged his team in the work. He said that they would like to get the complete answers to all the problems; though getting closer to that goal, they realized that there were plenty of hurdles in front of them. They hoped that the results they had obtained, when added to the information available by other methods and from other sources, would get them further to that complete understanding which would lead to accurate diagnosis ultimately without the tests; that was his conception of the true goal in medicine.

Correspondence.

STREPTOMYCIN AND PHARMACEUTICAL BENEFITS.

SIR: On my return from the Eleventh Conference of the International Union against Tuberculosis and the First International Congress on Diseases of the Chest held in Copenhagen and Rome respectively during September of this year, I was interested to notice the letters of Dr. Cotter Harvey, Dr. Bayliss and Dr. White in your issue of September 2 and of Dr. Munro Ford of September 23.

At both the above congresses considerable discussion on the subject of chemotherapy in tuberculosis showed the increasing apprehension of all tuberculosis workers as the result of the widespread and indiscriminate use of streptomycin and of PAS in the treatment of tuberculosis. It has been clearly demonstrated that even when combinations of drugs are employed, tubercle bacilli become resistant to both streptomycin and to PAS, and that no system of combined therapy at present employed prevents the appearance of resistant strains at some time during treatment. However, bacterial resistance appears far more rapidly to streptomycin alone than to PAS, and the higher the dosage of either or both drugs, the more rapid is the development of clinical resistance to therapy. Therefore, a very strong body of opinion overseas has crystallized the situation by emphasizing the use of the minimal effective doses of these drugs for the minimal effective period, pointing out the advantage which is thereby gained in that courses may be repeated at intervals, if necessary, and their therapeutic effect retained.

On the basis of these opinions, and the dosage of PAS recommended by Dr. Lehmann and his co-workers, the optimal dose of PAS appears to be 10 grammes of the acid daily in four divided doses. The effective dose of streptomycin appears to be 0·5 gramme per day in one single injection, but most Scandinavian workers are of the opinion that streptomycin, even in combination with PAS, should be reserved as an emergency "booster" agent and should not be employed as a routine chemotherapeutic agent. If streptomycin is employed in this manner, the appearance of drug-resistant organisms is even further delayed than if it be employed as a routine agent, and would appear to be the logical sequel to the observations already made.

At both congresses it was further emphasized that it is only in rare instances that chemotherapy alone will produce permanent arrest of pulmonary disease, and that its effect must, in most cases, be augmented by ancillary forms of treatment such as thoracoplasty, artificial pneumothorax *et cetera*. Where chronic bilateral fibro-cavernous disease precludes the use of such methods, the prospects of permanent benefit are remote, and the danger of the persistent excretion of drug-resistant organisms is greatly increased and constitutes a public health problem of major importance.

I would, therefore, join with the previous correspondents in urging care and discrimination in the selection of patients to whom streptomycin is administered, and view with considerable alarm the fact that this drug may now be employed indiscriminately in cases of tuberculosis.

Yours, etc.,

ALAN H. PENINGTON,
Specialist in Tuberculosis,
Repatriation Commission
Headquarters.

St. Kilda Road,
Melbourne,
October 3, 1950.

RHEUMATIC DISEASES.

SIR: Your reviewer (September 16, 1950, page 447) noted that G. D. Kersley omitted any mention of Reiter's disease in the latest edition of his book, "The Rheumatic Diseases". The raising of this symptom-complex to the status of a disease undermines the foundations of the accepted classification of rheumatic diseases and leaves nothing constructive in its stead. Almost any infection may be followed by arthritis, which may involve one or many joints in acute, subacute or chronic inflammation. Infections of the bowel and the urethra are especially likely to be thus complicated. In 1858 Coulson wrote that arthritis could follow suppuration in the urethra from any cause. According to Lorimer (1884), the first man to recognize that arthritis might result from non-gonococcal urethritis was Elliotson, whose career finished about 1840.

In Reiter's case (1916) diarrhœa appeared first, and urethritis, arthritis and conjunctivitis later; he declared it to be due to a spirochætal infection. Short (1947) observed in the United States Army that urethritis often accompanied dysenteric arthritis.

In Finland during an epidemic of Flexner dysentery, Paronen (1948) saw 344 cases of arthritis with urethritis in patients who had had dysentery. By writers in other parts of the world the syndrome has been attributed to many different organisms; and in many of the reported cases the urethritis was gonococcal. Thus there is no evidence of specificity of infection.

Ocular complications are not peculiar to post-urethritic arthritis, though there seems to be some special association reminiscent of that between iritis and ankylosing spondylitis. Godtfredsen (1949) says that conjunctivitis or iritis occurs in 10% of cases of rheumatic fever, and keratitis or iritis in 15% of cases of chronic polyarthritis. Conjunctivitis was the commonest eye lesion in Paronen's series, but keratitis and iritis were seen also.

This syndrome is merely an example of non-specific polyarthritis precipitated by urethritis, and it presents features known previously as manifestations of rheumatism due to other infections and to unknown causes.

Yours, etc.,

34 Queens Road,
Melbourne,
October 2, 1950.

M. KELLY.

References.

Coulson, W. (1858), "On Affections of the Joints following Operation on Genito-Urinary Organs", *British Medical Journal*, page 106.

Godtfredsen, E. (1949), "Pathogenesis of Concurrent Eye and Joint Diseases", *The British Journal of Ophthalmology*, Volume XXXIII, page 261.

Lorimer (1884), *British Medical Journal*, Volume II, page 269.

Paronen, I. (1948), "Reiter's Disease: A Study of 344 Cases Observed in Finland", *Acta medica Scandinavica*, Volume CXXXI, Supplement 212, pages 1-114.

Reiter, H. (1916), *"Ueber ein bisher unnerkannte Spirochäteninfektion (Spirochætosis arthritica)", Deutscher medizinische Wochenschrift*, Volume XLII, page 1535.

Short, C. L. (1947), "Arthritis in the Mediterranean Theatre of Operations. III. Clinical Description of Infectious and Other Types of Arthritis", *The New England Journal of Medicine*, Volume CCXXXVI, page 468.

LEUCOTOMY AND CHRONIC PSYCHOSIS.

SIR: The letter from Dr. Frank in today's issue may be supported to this extent: that mental illness is largely defined, in practice, in terms of social fitness, and such illness is largely determined by social factors. Also, research should be directed to elucidating and controlling such factors. This does not mean, surely, that we must limit treatment to social manipulations, for then all risky treatment could be called in question, at least in chronic psychosis.

Your correspondent's claim, from comparative anatomy, that the frontal lobe may be the highest endowment of man is no more substantiated, when bulk measurements are considered, than the claims of other as yet more "silent" areas, forming the bulk of the parietal and temporal lobes. In fact present evidence suggests these latter as more important for intelligence, in the psychologist's sense of an adaptive performance rating.

The evidence of degradation by gross frontal destruction is not an ultimate argument against partial frontal destruction. It is true that some increase of social irresponsibility is to be expected, but it is precisely those with too strict a social code—their tyrannical super-ego, as it were, incapacitating the ego—who are the patients most benefited by selective frontal lesions.

Every grave medical measure leaves "scars" on the personality, the *milieu interne* and, grossly or otherwise, on the anatomy, as far as our evidence goes. Social considerations may weigh as heavily on the orthopædic surgeon considering amputation or joint fixation, as on the neurosurgeon undertaking leucotomy, topectomy, or destruction of a tract or centre, cortical or otherwise, for relief of physical pain. The orthopædic surgeon is, in a humble way, reversing evolution, and so are all of us who condemn, say, an epileptic to take phenobarbitone for life—a drug which follows Hughlings Jackson's law of evolution reversal, perhaps more surely than the leucotomist.

While we do not know the results of castration or partial liver resection in chronic psychosis, we should advocate their use if results were as promising as those of leucotomy appear to be in competent hands, just as we should support splenectomy for malaria if it offered the best chance available of saving life or reason.

As to the indications for operation—I will refer only to one group of psychotics (and neurotics—their distinction from psychotics is irrelevant here) by quoting Professor Kennedy, of Durham, as accurately as I can recall his words:

> To withhold leucotomy from a hopelssly agitated obsessive is as surely malpractice as withholding appendicectomy in emergency. Legal risks and obligations are present in both cases, in England just as in Australia; but in each case there must be competent deliberation and decision, not avoidance of the issue on the basis of legal scruples.

Yours, etc.,

Mental Hospital,
Gladesville,
New South Wales.
September 30, 1950.

DOUGLAS EVERINGHAM.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Lectures and Demonstrations at Balmoral Naval Hospital.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that Dr. I. Douglas Miller will discuss "Traumatic Lesions of the Spine" on Tuesday, October 17, 1950, at 2 p.m., at the Balmoral Naval Hospital, Balmoral, Sydney. A clinical demonstration by members of the hospital staff will take place at 4 p.m.

On Tuesday, November 14, 1950, at 2 p.m., Dr. W. Wilson Ingram will speak on "The Diagnosis and Treatment of the Glycosurias".

All members of the medical profession are invited to attend these sessions, which are held at monthly intervals throughout the year.

Medical Societies.

THE MEDICAL SCIENCES CLUB OF SOUTH AUSTRALIA.

A MEETING of the Medical Sciences Club of South Australia was held in the Anatomy Lecture Theatre, Frome Road, Adelaide, on September 1, 1950.

Stomatal Movements.

DR. F. L. MILTHORPE presented a paper on the mechanism and biological significance of stomatal movements. He said that stomata were dynamic organs occurring on the leaf surface. Each consisted of a pore enclosed by two guard cells, which changed in volume and thereby altered the size of the pore. The changes in volume were due to a turgor, not to a cell-wall, mechanism. The current hypothesis of the mechanism was that, in response to light, the acidity of the cells was decreased owing to removal of carbon dioxide or change in organic acid content and/or composition; that shifted the equilibrium of starch-sugar balance, there was an increase in osmotic concentration, water entered and the pore opened. The evidence of starch content and changes in aperture had been examined; it had been shown that similar diurnal rhythms existed with both, but they were not directly correlated. Some stomata, for example, those of the onion, responded normally to light, but contained no starch. The postulation of hexose-1-phosphate as the soluble compound involved, although supported by the known effect of change of pH on equilibrium change and by the demonstration of phosphorylase in guard cells, was still entirely theoretical. The exact nature of the turgor mechanism in stomatal movement, therefore, still remained unknown. There was large light effect which was not associated with changes in carbon dioxide concentration. Turgor changes in the other epidermal cells were more important than hitherto thought—stomal movement resulting from those was probably related more to rates of turgor change than to absolute values.

Dr. Milthorpe went on to say that the stomata played an important role in regulating the rate of water loss from leaves. They were regulatory over the entire range under most conditions, but in still air the resistance of vapour shells over the leaf was much greater than stomatal resistance—there they were therefore regulatory only over part of the range. Earlier work on the diffusion through pores had neglected the "leaf" resistance, leading to false assumptions. They were regulatory in another sense—namely, that they closed in response to wind. Increase in wind velocity had little effect on transpiration rates—at least, it was far from proportional to the increased vapour pressure gradient. That stomatal closure with wind was a response to lower humidity and to increased carbon dioxide concentration; it was accentuated by a period of wilting and was possibly associated with an increase in the permeability of the guard cell walls to carbon dioxide.

Stomata played an important regulatory role in plant life. They regulated the passage of two gases—carbon dioxide and water vapour. When ample water was available they opened widely and, at the expense of reducing the available water supply, allowed as much carbon dioxide to enter as possible; when water supply was short, they closed and conserved water at the expense of reduced assimilation and growth.

Obituary.

PATRICK JAMES KERWIN.

We are indebted to Dr. L. M. McKillop for the following appreciation of the late Dr. Patrick James Kerwin.

The death occurred in Brisbane on September 4, 1950, of Dr. Patrick James Kerwin, after a short final illness, from cardiac failure at the age of seventy-seven years. Dr. Kerwin, who was born in Ireland, obtained the qualifications of L.R.C.S. and L.R.C.P. (Edin.), L.F.P.S.G. (Glasgow). He reached Sydney in the sailing ship *Buckingham* in 1902 and settled in practice at Irvinebank, in North Queensland. There he married Miss Mary Walsh, and he leaves one child, Neil, who is the wife of Mr. D. C. Gordon-Duff, a successful tea planter in Ceylon. Mrs. Kerwin predeceased her husband in 1943. After leaving Irvinebank Dr. Kerwin practised for some years in Cairns, and in 1915 came to Brisbane and joined the staff of the 13th Australian General Hospital at Enoggera, where I was associated with him. In 1917 he began private practice in Brisbane. In 1940 he reentered the army as a major and served at various camps about Brisbane. He latterly joined the Commonwealth Health Department in Brisbane as a medical officer. Dr. Kerwin, who was of independent means, was, in every sense of the word, a typical Irish gentleman whom it was a privilege to know. His loss will be felt by a wide circle of friends in and outside of his profession. He had the knack of making friendships and of retaining them. He was a keen fisherman. During the regime of the Moore Government in Queensland Dr. Kerwin was elected as member for Merthyr electorate.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

The undermentioned have been registered, pursuant to the provisions of the *Medical Practitioners Act*, 1938-1945, of New South Wales, as duly qualified medical practitioners:

Ackland, Raydon William, M.B., B.S., 1949 (Univ. Melbourne), c.o. Dr. I. MacGillivray, Murwillumbah.

Chambers, Ella, M.A., B.Ch., 1927 (Q.U. Belfast), North Haven, via Laurieton.

Drury-White, Jean Mary, M.B., B.S., 1939 (Univ. London), District Hospital, Broken Hill.

Egan, John Celestine, M.B., B.S., 1946 (Univ. Melbourne), St. Margaret's Hospital, Sydney.

Fields, Kim, registered in accordance with the provisions of Section 17 (1) (*c*) of the *Medical Practitioners Act*, 1938-1945, District Hospital, Lithgow.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED SEPTEMBER 23, 1950.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.[2]	Australian Capital Territory.	Australia.[3]
Ankylostomiasis	*	..	..	..	..	..	..	..	..
Anthrax	*	..	..	..	..	..	..	..	..
Beriberi	*	*	*	*	*	*	..	*	..
Bilharziasis	*	..	..	..	..	..	..	..	..
Cerebro-spinal Meningitis	4(1)	2(2)	2(1)	..	1	1	..	..	10
Cholera	..	..	..	..	..	..	..	..	..
Coastal Fever(*a*)	*	*	..	*	*	*	*	*	..
Dengue	*	*	*	*	*	*	..	*	..
Diarrhœa (Infantile)	..	..	2(2)	..	..	..	..	..	2
Diphtheria	9(6)	3(2)	5(4)	1(1)	1	1(1)	..	..	20
Dysentery (Amœbic)	*	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	*	1(1)	4(3)	..	1(1)	..	..	..	6
Encephalitis Lethargica	..	..	..	..	..	..	..	..	..
Erysipelas	*	*	*	2(1)	*	*	..	..	2
Filariasis	*	..	..	..	..	..	..	..	..
Helminthiasis	*	..	*	*	*	*	*	*	..
Hydatid	*	..	*	*	..	*	*	..	..
Influenza	*	*	*	..	*	*	..	*	..
Lead Poisoning	*	*	..	*	*	*	*	*	..
Leprosy	..	..	..	..	..	..	..	..	..
Malaria(*b*)	*	..	..	..	..	..	..	..	..
Measles	*	*	*	311(257)	*	*	..	3	314
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	18(13)	2(1)	1	2(2)	3(1)	1	*	3	30
Psittacosis	*	..	*	..	*	*	*	*	..
Puerperal Fever	..	..	..	..	..	..	..	..	..
Rubella(*c*)	*	*	..	*	..	*	..	2	2
Scarlet Fever	10(9)	18(9)	12(5)	8(3)	1(1)	1(1)	..	..	50
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	*	..	4(2)	*	*	*	*	*	4
Trachoma	*	..	*	*	*	*	*	*	..
Tuberculosis(*d*)	30(18)	14(11)	15(11)	6(4)	13(9)	7(5)	..	..	85
Typhoid Fever(*e*)	..	..	1(1)	..	..	..	..	..	1
Typhus (Endemic)(*f*)	..	..	1(1)	..	..	..	..	..	1
Undulant Fever	..	1	..	..	..	..	..	..	1
Weil's Disease(*g*)	*	*	..	*	*	*	*	*	..
Whooping Cough	*	*	*	7(5)	*	*	..	..	7
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] The form of this table is taken from the *Official Year Book of the Commonwealth of Australia*, Number 37, 1946–1947. Figures in parentheses are those for the metropolitan area.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from the Northern Territory.
* Not notifiable.
(*a*) Includes Mossman and Sarina fevers. (*b*) Mainly relapses among servicemen infected overseas. (*c*) Notifiable disease in Queensland in females aged over fourteen years. (*d*) Includes all forms. (*e*) Includes enteric fever, paratyphoid fevers and other Salmonella infections. (*f*) Includes scrub, murine and tick typhus. (*g*) Includes leptospiroses, Weil's and para-Weil's disease.

Cohn, Lotar, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1945, Auxiliary Hospital, Randwick.

Frank, Chana Halina, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1945, 25 Bayswater Road, Darlinghurst.

Gries, Leon, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1945, Waterfall Sanatorium, Waterfall.

Jacobi, Marian, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1945, Mental Hospital, Orange.

Niedzinski, Jozef, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1945, 79 Ocean Street, Woollahra.

Sonnabend, Samuel Isaac, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1945, District Hospital, Parramatta.

Streimer, Ludwig, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1945, 16 Botany Street, Bondi Junction.

Weintraub, Saul, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1945, District Hospital, Wallsend.

The following additional qualifications have been registered:

Bellmaine, Stanley Percy, 141 Macquarie Street, Sydney (M.B., B.S., 1933, Univ. Sydney, D.C.H., R.C.P. and S., England, 1939), M.R.A.C.P., 1949.

Morgan, David Ross, Mental Hospital, Orange (M.B., B.S., 1942, Univ. Sydney), D.P.M., 1950 (Univ. Sydney).

Watts, Archibald William James, 53 McIntosh Street, Gordon (M.B., B.S., 1943, Univ. Sydney, M.Ch. (Orth.), 1949, Univ. Liverpool), F.R.A.C.S., 1950, M.S., 1950 (Univ. Sydney).

QUEENSLAND.

THE undermentioned have been registered, pursuant to the provisions of *The Medical Acts*, 1939 to 1948, of Queensland, as duly qualified medical practitioners:

Were, Stuart Owen Mansel, M.B., B.S., 1946 (Univ. Melbourne), Commonwealth Health Laboratory, Rockhampton.

McGladdery, Joseph Percy, M.B., B.S., 1936 (Univ. London), M.D., 1939 (Univ. London), M.R.C.P. (London), 1947, D.P.H., 1939 (Univ. London), c.o. G.P.O., Brisbane.

The following additional qualifications have been registered:

Stable, Grantley Sheridan, Dennis Street, Indooroopilly, Brisbane, D.C.H., R.C.P. and S. (London), 1950.

Wilkinson, Cyril Ignatius, Q.N. Bank Building, Fortitude Valley, F.R.C.S. (Ireland), 1948.

Corrigenda.

IN the paper by T. E. Lowe, published in the issue of September 30, 1950, a paragraph entitled "Errata" is published at the end of the paper. This paragraph should not have appeared as the figures in the blocks concerned are correct.

IN the paper by David A. Sugerman entitled "Observations on the Vertebral and Basilar Arteries and their Branches in Man, with Special Reference to the Lateral Parolivary Fossa", which appeared in the issue of September 9, 1950, at page 402, the legends to Figures II to VIII inclusive were included unintentionally; the words "supraolivary area" in the legends to Figures II, III, IV, V and VIII should read "lateral parolivary fossa". The last two lines of paragraph 3 of the "Summary" on page 406 should read "ing gross asymmetries of calibre of either the vertebral or the posterior cerebral arteries (or both)".

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Pittorino, Anthony Joseph, M.B., B.S., 1950 (Univ. Sydney), St. Joseph's Hospital, Auburn.

Medical Appointments.

Dr. P. L. K. Addison has been appointed a member of the Railway Service Superannuation Board of New South Wales.

Diary for the Month.

OCT. 16.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.
OCT. 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.
OCT. 18.—Western Australian Branch, B.M.A.: General Meeting.
OCT. 19.—New South Wales Branch, B.M.A.: Clinical Meeting.
OCT. 19.—Victorian Branch, B.M.A.: Executive Meeting.
OCT. 24.—New South Wales Branch, B.M.A.: Ethics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney)—All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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